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=> d his full

      FILE 'REGISTRY' ENTERED AT 11:30:23 ON 10 FEB 2003
                E AZITHROMYCIN/CN
L15             1 SEA ABB=ON  AZITHROMYCIN/CN

     FILE 'HCAPLUS' ENTERED AT 11:30:47 ON 10 FEB 2003
L16          1703 SEA ABB=ON  L15
L17            64 SEA ABB=ON  L16 AND (?SINGLE? OR ONE?(W)?TIME? OR ?ONCE?)(W)(?D
                  OSE? OR ?DOSAGE?)
L18             3 SEA ABB=ON  L17 AND (?OTITIS?(W)?MEDIA? OR ?MIDDLE?(W)EAR?)
                  D TI 1-3
                  D AU 1-3
L19            42 SEA ABB=ON  L16 AND (?OTITIS?(W)?MEDIA? OR ?MIDDLE?(W)EAR?)
L20             3 SEA ABB=ON  L17 AND (?RESPIRAT? OR ?BREATH?)(W)(?INFECT? OR
                  ?DISEAS?)
L21             0 SEA ABB=ON  L17 AND (E OR ?ENTEROCOCCUS?)(W)?FAECALIS?
L22             0 SEA ABB=ON  L17 AND ?ENTEROCOCCUS?(W)?FAECALIS?
L23             6 SEA ABB=ON  L18 OR L20


     FILE 'HCAPLUS' ENTERED AT 11:46:47 ON 10 FEB 2003
L24             0 SEA ABB=ON  L17 AND (E OR ?ENTEROCOCC?)(W)(?FAECALIS? OR
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L25             6 SEA ABB=ON  L18 OR L20 OR L24

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO' ENTERED AT
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     FILE 'HCAPLUS' ENTERED AT 11:49:07 ON 10 FEB 2003
L26          1965 SEA ABB=ON  L15 OR ?AZITHROMYCIN?
L27            73 SEA ABB=ON  L26 AND (?SINGLE? OR ONE?(W)?TIME? OR ?ONCE?)(W)(?D
                  OSE? OR ?DOSAGE?)
L28             7 SEA ABB=ON  L27 AND ((?RESPIRAT? OR ?BREATH? OR ?MIDDLE?(W)EAR?
                  )(W)(?INFECT? OR ?DISEAS?) OR ?OTITIS?(W)?MEDIA? OR (E OR
                  ?ENTEROCOCC?)(W)(?FAECALIS? OR ?FACALIS? OR ?FECALIS?))
                                                    7 cits  - attached


     FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO' ENTERED AT
     11:57:02 ON 10 FEB 2003
L29            39 SEA ABB=ON  L28
L30            20 DUP REMOV L29 (19 DUPLICATES REMOVED)  20 acti - attached
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=> d que stat l28
L15             1 SEA FILE=REGISTRY ABB=ON  AZITHROMYCIN/CN
L26          1965 SEA FILE=HCAPLUS ABB=ON  L15 OR ?AZITHROMYCIN?
L27            73 SEA FILE=HCAPLUS ABB=ON  L26 AND (?SINGLE? OR ONE?(W)?TIME? OR
                  ?ONCE?)(W)(?DOSE? OR ?DOSAGE?)
L28             7 SEA FILE=HCAPLUS ABB=ON  L27 AND ((?RESPIRAT? OR ?BREATH? OR
                  ?MIDDLE?(W)EAR?)(W)(?INFECT? OR ?DISEAS?) OR ?OTITIS?(W)?MEDIA?
                   OR (E OR ?ENTEROCOCC?)(W)(?FAECALIS? OR ?FACALIS? OR ?FECALIS?
                  ))

=> d ibib abs hitrn l28 1-7

L28  ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:141726  HCAPLUS
DOCUMENT NUMBER:          136:363132
TITLE:                    Azithromycin in children: A critical review
                          of the evidence
AUTHOR(S):                Pacifico, Lucia; Chiesa, Claudio
CORPORATE SOURCE:         Institute of Pediatrics, La Sapienza University of
                          Rome, Rome, Italy
SOURCE:                   Current Therapeutic Research (2002), 63(1), 54-76
                          CODEN: CTCEA9; ISSN: 0011-393X
PUBLISHER:                Excerpta Medica, Inc.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   This review explores the use of azithromycin in the treatment of
     pediatric infections.  Azithromycin is a macrolide antibiotic
     that can be dosed once daily.  In the last decade, the body of literature
     concerning the clin. applications of azithromycin has grown
     rapidly, leading to improved understanding as well as new questions about
     the role of this drug in the treatment of adult and pediatric infections.
     We conducted a MEDLINE literature search to identify pertinent
     English-language studies of azithromycin published between 1987
     and 2001.  The use of azithromycin in the treatment of acute
     Streptococcus pyogenes pharyngotonsillitis, acute otitis
     media, community-acquired pneumonia, pertussis, skin and soft
     tissue infections, Mycobacterium avium complex (MAC), trachoma, typhoid
     fever, cat-scratch disease, cryptosporidiosis, and legionnaires' disease
     has been studied in clin. trials.  Azithromycin is indicated as
     a first-line treatment for respiratory tract infections caused by
     Legionella species, Mycoplasma pneumoniae, and Chlamydia pneumoniae, and
     as empiric therapy for community-acquired pneumonia in older children and
     adolescents who are deemed appropriate for outpatient oral therapy.
     Azithromycin in a single dose is an excellent
     treatment for chlamydia cervicitis/urethritis and for trachoma and has
     demonstrated efficacy in prophylaxis and treatment of disseminated MAC
     infections in children who have AIDS.  Azithromycin may be
     considered as an alternative in the treatment of skin and soft tissue
     infections, although local patterns of resistance of pathogens must be
     considered in its selection.
IT   83905-01-5, Azithromycin
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (azithromycin in treatment of pediatric infections)
REFERENCE COUNT:          99    THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L28 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:588168 HCAPLUS
DOCUMENT NUMBER: 134:50858
TITLE: Short-course antimicrobial therapy for upper respiratory tract infections
AUTHOR(S): Guay, David R. P.
CORPORATE SOURCE: Institute for the Study of Geriatric Pharmacotherapy, College of Pharmacy, and PartneringCare Senior Services, HealthPartners, University of Minnesota, Minneapolis, MN, USA
SOURCE: Clinical Therapeutics (2000), 22(6), 673-684
CODEN: CLTHDG; ISSN: 0149-2918
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 62 refs. This review examines the issues surrounding short-course antimicrobial therapy of group A beta-hemolytic streptococcal (GABHS) tonsillopharyngitis, acute (suppurative) **otitis media**, and acute sinusitis. Accumulating evidence suggests that short-course (ie, .ltoreq.5 days) antimicrobial therapy may have equiv. or superior efficacy compared with traditional longer (10- to 14-day) therapies. In GABHS tonsillopharyngitis, short-course therapy with 6 days of amoxicillin, 4 or 5 days of various cephalosporins, and 5 days of **azithromycin** (10 mg/kg once daily on all 5 days in pediatric patients) are all reasonable alternatives to traditional 10-day penicillin therapy. In uncomplicated acute (suppurative) **otitis media, single-dose** i.m. ceftriaxone or 3- to 5-day short-course oral antimicrobial therapy should be effective in .gtoreq.80% of patients. However, more research is needed in children aged <2 yr, since short-course therapy may not be successful in most patients in this population. In sinusitis, most short-course therapy data have involved acute maxillary disease in adult patients. Preliminary results are encouraging, but more study is needed, esp. in children. Cost-containment in antimicrobial therapy should include consideration of short-course therapy in the management of upper respiratory tract infections.
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:617434 HCAPLUS
DOCUMENT NUMBER: 129:310708
TITLE: A phase I determination of **azithromycin** in plasma during a 6-week period in normal volunteers after a standard dose of 500 mg once daily for 3 days
AUTHOR(S): Crokaert, F.; Hubloux, A.; Cauchie, P.
CORPORATE SOURCE: Institut Jules Bordet, Brussels, Belg.
SOURCE: Clinical Drug Investigation (1998), 16(2), 161-166
CODEN: CDINFR; ISSN: 1173-2563
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacokinetics of **azithromycin** were evaluated in 12 healthy volunteers. Participants received a **single dose** of 2 .times. 250 mg **azithromycin** administered orally in the fasting state with 240 mL water on 3 consecutive days. **Azithromycin** was present in measurable levels in plasma (>5

.mu.g/L) for 7-17 days after the beginning of treatment. The apparent elimination half-life was very long (obsd. range: 49-108 h, i.e. .apprx.2-4.5 days). From the results in plasma, one can extrapolate that the **azithromycin** concn. would remain >1 .mu.g/L (corresponding to concns. in tissues >0.1 mg/L) for 15-30 days following treatment. The elimination half-life of **azithromycin** (av. of 76 h) was in agreement with values of depletion rates in tissues corresponding to a half-life of 60-72 h. The utility of the long exposure of patients with benign **respiratory infections** to **azithromycin** and to subinhibitory concns. of **azithromycin** should be questioned.

IT **83905-01-5, Azithromycin**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase I detn. of **azithromycin** in plasma during 6-wk period in normal volunteers after std. dose of 500 mg)

L28 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:725247 HCAPLUS
DOCUMENT NUMBER: 126:14371
TITLE: Comparative study of once-weekly **azithromycin** and once-daily amoxicillin treatments in prevention of recurrent acute **otitis media** in children
AUTHOR(S): Marchisio, Paola; Principi, Nicola; Sala, Emanuela; Lanzoni, Luisa; Sorella, Stefania; Massimini, Alessandra
CORPORATE SOURCE: Dep. Pediatrics, Univ. Milan Med. Sch., Milan, 20157, Italy
SOURCE: Antimicrobial Agents and Chemotherapy (1996), 40(12), 2732-2736
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Continuous chemoprophylaxis is effective in the prevention of new episodes of acute **otitis media** (AOM) in otitis-prone children, but compliance can be a problem and thus efficacy can be decreased. Intermittent chemoprophylaxis has so far shown conflicting results. **Azithromycin**, which has a peculiar pharmacokinetics, resulting, even after a **single dose**, in persistently elevated concns. in respiratory tissues, could permit a periodic administration with higher compliance. We compared a 6-mo course of once-weekly **azithromycin** (5 or 10 mg/kg of by wt.) with that of once-daily amoxicillin (20 mg/kg) in a single-blind, randomized study of prophylaxis for recurrent AOM in 159 children aged 6 mo to 5 yr with at least three episodes of AOM, while in the 10-mg/kg **azithromycin** group, 11 (14.9%) of 74 children experienced 15 episodes. The 5-mg/kg/wk **azithromycin** trial was prematurely interrupted after nine cases, due to the high occurrence rate of AOM (55.5%). During the 6-mo prophylaxis period, the proportion of children with middle ear effusion declined similarly in both groups. No substantial modification of the nasopharyngeal flora was noted at the end of prophylaxis in both antimicrobial groups. In the 6-mo-postprophylaxis follow-up period, about 40% of children in both groups again developed AOM. **Azithromycin** at 10 mg/kg once weekly can be regarded as a valid alternative to once-daily low-dose amoxicillin for the prophylaxis of AOM. Although in the present study no microbiol. drawback was noted, accurate selection of

children eligible for prophylaxis is mandatory to avoid the risk of emergence of resistant strains.

IT **83905-01-5, Azithromycin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**azithromycin** and once-daily amoxicillin treatments in prevention of recurrent acute **otitis media** in children)

L28 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:437159 HCAPLUS
DOCUMENT NUMBER: 125:75506
TITLE: Penetration of **azithromycin** into middle ear effusions in acute and secretory **otitis media** in children
AUTHOR(S): Pukander, J.; Rautianen, M.
CORPORATE SOURCE: Department of Otolaryngology, University of Tampere Medical School, Tampere, FIN-33101, Finland
SOURCE: Journal of Antimicrobial Chemotherapy (1996), 37(Suppl. C, Azithromycin: Further Clinical Experience), 53-61
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In an open-label study, the concns. of **azithromycin** in middle ear effusions and plasma were detd. in 29 children between 1 and 8 yr of age with a diagnosis of either secretory **otitis media** of at least 1 mo's duration or acute **otitis media**. **Azithromycin** (10 mg/kg) was administered as a **single dose** 12, 24, or 48 h before the insertion of tympanostomy tubes to 17 children with secretory **otitis media** and once daily for 5 days (10 mg/kg on day 1, 5 mg/kg on days 2-5) to 12 children with acute **otitis media**. In the 16 evaluable patients with secretory **otitis media, azithromycin** penetrated middle ear effusions, with group mean concns. approx. two orders of magnitude greater than the concurrent plasma concns. 12, 24, and 48 h after administration. Similar plasma:effusion ratios were found 24 and 48 h after starting once-daily therapy in 10 evaluable patients with acute **otitis media**.

IT **83905-01-5, Azithromycin**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(penetration of **azithromycin** into middle ear effusions in acute and secretory **otitis media** in children)

L28 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:87437 HCAPLUS
DOCUMENT NUMBER: 124:164358
TITLE: Therapeutic activity and local delivery of **azithromycin** in animal models of local infection
AUTHOR(S): Matsunaga, Toshiyuki; Shimohira, Hiroshi; Ogawa, Masatoshi; Sawada, Yasufusa; Muto, Hideya; Enogaki, Kazunori; Shimooka, Kino
CORPORATE SOURCE: New Prod. Dev. Cent., Pfizer Pharm. Inc., Aichi,

470-23, Japan
SOURCE: Nippon Kagaku Ryoho Gakkai Zasshi (1995), 43(Suppl. 6), 95-9
CODEN: NKRZE5; ISSN: 1340-7007
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB We compared the therapeutic efficacy of **azithromycin** (AZM), in several localized infection models, with those of clarithromycin (CAM), tosufloxacin (TFLX) and cefaclor (CCL). Local delivery of AZM and CAM to infection sites was also studied. In a rat pouch infection with Staphylococcus aureus, 30 mg/kg doses of AZM at 0, 6, and 24 h post-challenge reduced the CFU by approx. 99% from the initial inoculum. Although the MIC of AZM was 4 and 16 fold higher than that of CAM and TFLX, resp., AZM demonstrated greater therapeutic efficacy than CAM and TFLX. In a murine model of s.c. infection with Streptococcus pyogenes, 25 mg/kg (twice a day) doses of AZM at 1 and 2 days post-challenge produced a 99% redn. of CFU as compared to an untreated control. These effects of AZM were much greater than those of CAM, even though CAM exhibited greater in vitro potency. In a murine **respiratory infection** model with Haemophilus influenzae, a **single dose** of AZM (50 mg/kg) at 4 h post-challenge significantly ($p < 0.01$) reduced the CFU as compared with CAM and the untreated control. AZM produced more than 40 times higher concns. in lungs than in serum, and the lung concns. exceeded the MIC for the pathogen until at least 48 h post-dosing. Lung concns. of AZM in infected mice were significantly ($p < 0.01$) higher than in non-infected mice. These results suggest that AZM may have good clin. efficacy in localized human infections because of its high, and prolonged, levels in tissues.

IT **83905-01-5, Azithromycin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(therapeutic activity and local delivery of **azithromycin** in local infection)

L28 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:87428 HCAPLUS
DOCUMENT NUMBER: 124:164186
TITLE: Pharmacokinetics of **azithromycin** and its clinical results
AUTHOR(S): Aoki, Nobuki
CORPORATE SOURCE: Dep. Intern. Med., Shinrakuen Hosp., Niigata, 950-21, Japan
SOURCE: Nippon Kagaku Ryoho Gakkai Zasshi (1995), 43(Suppl. 6), 234-8
CODEN: NKRZE5; ISSN: 1340-7007
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB **Azithromycin** (AZM), a new oral azalide antibiotic, was p.o. administered to 5 aged patients with various disturbances of renal function at a **single dose** of 500 mg, to examine its blood concn. and urinary excretion rate. The degree of renal disturbance was graded as mild (Group I) in 1 case, moderate (Group II) in 1 case and severe (Group III) in 3 cases for comparison of the pharmacodynamics in individual groups. The elimination half-life in blood was revealed to be 45.4 h in Group I, 30.5 h in Group II, and 29.7 h in Group II (mean values). The area under the blood concn. time curve (AUC) was 3.83, 4.21, and 4.66 .mu.g.h/mL in Groups, I, II, and III, resp. The excretion rate

in accumulated urine samples of up to 120 h after administration was 5.57% in Group I, 5.53% in Group II and 4.62% in group III. AZM was used in 6 patients with **respiratory infection**, including 1 case of chronic bronchitis, 2 of bronchiectasia + infection and 3 of bronchial asthma + infection. The result was evaluated to be good in all 6 cases. There were no adverse reactions or abnormal lab. values thought to be due to the drug during the study period. Thus, the drug was considered to be a useful agent for treating **respiratory infection**.

IT **83905-01-5, Azithromycin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetics of **azithromycin** in humans with renal failure, and its clin. effect on **respiratory infection**)

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=> d que stat l30
L15             1 SEA FILE=REGISTRY ABB=ON  AZITHROMYCIN/CN
L26          1965 SEA FILE=HCAPLUS ABB=ON  L15 OR ?AZITHROMYCIN?
L27            73 SEA FILE=HCAPLUS ABB=ON  L26 AND (?SINGLE? OR ONE?(W)?TIME? OR
                  ?ONCE?)(W)(?DOSE? OR ?DOSAGE?)
L28             7 SEA FILE=HCAPLUS ABB=ON  L27 AND ((?RESPIRAT? OR ?BREATH? OR
                  ?MIDDLE?(W)EAR?)(W)(?INFECT? OR ?DISEAS?) OR ?OTITIS?(W)?MEDIA?
                   OR (E OR ?ENTEROCOCC?)(W)(?FAECALIS? OR ?FACALIS? OR ?FECALIS?
                  ))
L29            39 SEA L28
L30            20 DUP REMOV L29 (19 DUPLICATES REMOVED)

=> d ibib abs l30 1-20

L30  ANSWER 1 OF 20     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:    2002400562     MEDLINE
DOCUMENT NUMBER:     22144714   PubMed ID: 12150171
TITLE:               Impact of single dose
                     azithromycin on group A streptococci in the upper
                     respiratory tract and skin of Aboriginal children.
AUTHOR:              Shelby-James Tania M; Leach Amanda J; Carapetis Jonathan R;
                     Currie Bart J; Mathews John D
CORPORATE SOURCE:    Menzies School of Health Research, Darwin, Australia.
SOURCE:              PEDIATRIC INFECTIOUS DISEASE JOURNAL, (2002 May) 21 (5)
                     375-80.
                     Journal code: 8701858. ISSN: 0891-3668.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200211
ENTRY DATE:          Entered STN: 20020802
                     Last Updated on STN: 20021212
                     Entered Medline: 20021119
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AB BACKGROUND: Aboriginal children living in remote Australia experience high rates of bacterial infection such as trachoma, **otitis media** and streptococcal skin infection, which often progress to associated chronic diseases in later life. METHODS: In February, 1995, **single dose azithromycin** was given to 130 Aboriginal children with trachoma and their contacts. The impact of this

program on respiratory and skin group A Streptococcus pyogenes carriage and infection was also monitored. RESULTS: Immediately before treatment 90% of children had skin sores, 38% of sores had pus and 74% of sores with pus had group A Streptococcus (GAS). Overall 57% of children had GAS skin infections. At 2 to 3 weeks and 2 and 6 months after treatment, this proportion was 10, 32 and 51%, respectively. For the upper respiratory tract GAS recovery rates were 8% before treatment and 0, 11 and 15% at the 2- to 3-week, 2-month and 6-month posttreatment visits, respectively. Multiple types occurred concurrently in individuals, particularly after treatment. Identical types were sometimes recovered simultaneously from the upper respiratory tract and skin, suggesting that the high rates of acute rheumatic fever in this population in the absence of high rates of detectable throat GAS carriage could be related to high rates of skin GAS infection. CONCLUSIONS: There is an urgent need for education, adequate housing, scabies eradication and improved hygiene to reduce skin trauma and subsequent GAS infection in this population. Clinical trials are needed to determine how these measures can best be integrated with the trachoma eradication program to maximize health outcomes.

L30 ANSWER 2 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002142813 EMBASE
TITLE: How predictive is PK/PD for antibacterial agents?.
AUTHOR: Frimodt-Moller N.
CORPORATE SOURCE: N. Frimodt-Moller, Microbiological R and D, Statens Serum Institut, 5 Artillerivej, DK-2300 Copenhagen S, Denmark. nfm@ssi.dk
SOURCE: International Journal of Antimicrobial Agents, (2002) 19/4 (333-339).
Refs: 40
ISSN: 0924-8579 CODEN: IAAGEA
PUBLISHER IDENT.: S 0924-8579(02)00029-8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The pharmacodynamic (PD) parameters most often used in studies of antibiotic effect include the following relationships between the antibiotic concentration curve in serum as a surrogate marker for the antibiotic concentration at the infection site, the peak/minimal inhibitory concentration (MIC) ratio, the area under the curve (AUC)/MIC ratio and the duration of time the concentration exceeds the MIC (T(MIC)). The MIC plays an important role also as a PD marker, and its precision in this respect is discussed. The predictive role of T(MIC) is important for drugs showing minimal concentration dependent effect such as the .beta.-lactam antibiotics, the macrolides and others. The time can be calculated as the chronological time measured or as the (cumulative) per cent of the dosing interval covered by the dose. Several clinical studies have confirmed this relationship. It can be deduced from experimental as well as clinical studies that there is a minimal effective time (MET), which needs to be covered by the antibiotic concentration at the site of infection in order to achieve cure. Dosing according to this MET will result in the least antibiotic needed for the shortest duration. In several cases a **single dose** will suffice to cover the MET. If this is not possible the antibiotic should be dosed in a way, that each dose will surpass the MIC for at least 40-50% of the dosing interval.

For antibiotics with a clear concentration-dependent bacterial killing effect the most important pharmacokinetic/pharmacodynamic (PK/PD) index is the peak/MIC ratio (or the AUC/MIC ratio). This is the case for aminoglycosides and fluoroquinolones, and for both classes a peak/MIC ratio of at least 10 within the first 24 h of treatment has been shown to result in around 90% bacteriological as well as clinical cure. One consequence of clinical dosing has been the once-a-day (OD) dosing for aminoglycosides, which is the standard mode of therapy in many countries. Clinical studies in the field of antibacterial PD are still relatively scarce, and much information is needed to enable relevant dosing strategies for all types of antibiotics against all common infections and micro-organisms. Copyright .COPYRGT. 2002.

L30 ANSWER 3 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:465527 BIOSIS
DOCUMENT NUMBER: PREV200200465527
TITLE: **Single dose azithromycin** is safe and effective in the treatment of acute **otitis media**.
AUTHOR(S): Jorgensen, Daniel M. (1); McCoig, Cynthia C. (1); Benner, Rebecca J. (1); Dunne, Michael W. (1)
CORPORATE SOURCE: (1) Anti-Infectives, Pfizer Inc., New London, CT USA
SOURCE: Pediatric Research, (April, 2002) Vol. 51, No. 4 Part 2, pp. 284A. http://www.pedresearch.org/. print.
Meeting Info.: Annual Meeting of the Pediatric Societies' Baltimore, MD, USA May 04-07, 2002
ISSN: 0031-3998.
DOCUMENT TYPE: Conference
LANGUAGE: English

L30 ANSWER 4 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
ACCESSION NUMBER: 2002:162981 BIOSIS
DOCUMENT NUMBER: PREV200200162981
TITLE: **Azithromycin** in children: A critical review of the evidence.
AUTHOR(S): Pacifico, Lucia; Chiesa, Claudio (1)
CORPORATE SOURCE: (1) Institute of Pediatrics, La Sapienza University, Viale Regina Elena, 324, 00161, Rome: claudio.chiesa@uniromal.it Italy
SOURCE: Current Therapeutic Research, (January, 2002) Vol. 63, No. 1, pp. 54-76. print.
ISSN: 0011-393X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Background: **Azithromycin** is a macrolide antibiotic that can be dosed once daily. In the last decade, the body of literature concerning the clinical applications of **azithromycin** has grown rapidly, leading to improved understanding as well as new questions about the role of this drug in the treatment of adult and pediatric infections. Objective: This review explores the use of **azithromycin** in the treatment of pediatric infections. Methods: We conducted a MEDLINE literature search to identify pertinent English-language studies of **azithromycin** published between 1987 and 2001. Results: The use of **azithromycin** in the treatment of acute Streptococcus pyogenes pharyngotonsillitis, acute **otitis media**, community-acquired pneumonia, pertussis, skin and soft tissue infections, Mycobacterium avium complex (MAC), trachoma, typhoid fever, cat-scratch

disease, cryptosporidiosis, and legionnaires' disease has been studied in clinical trials. Conclusions: **Azithromycin** is indicated as a first-line treatment for respiratory tract infections caused by Legionella species, Mycoplasma pneumoniae, and Chlamydia pneumoniae, and as empiric therapy for community-acquired pneumonia in older children and adolescents who are deemed appropriate for outpatient oral therapy. **Azithromycin** in a **single dose** is an excellent treatment for chlamydia cervicitis/urethritis and for trachoma and has demonstrated efficacy in prophylaxis and treatment of disseminated MAC infections in children who have AIDS. **Azithromycin** may be considered as an alternative in the treatment of skin and soft tissue infections, although local patterns of resistance of pathogens must be considered in its selection.

L30 ANSWER 5 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002089491 EMBASE
TITLE: FDA approves **single-dose** Zithromax.
SOURCE: Infections in Medicine, (2002) 19/2 (50).
ISSN: 0749-6524 CODEN: INMDEG
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
011 Otorhinolaryngology
037 Drug Literature Index
LANGUAGE: English

L30 ANSWER 6 OF 20 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001037090 MEDLINE
DOCUMENT NUMBER: 20383741 PubMed ID: 10929916
TITLE: Short-Course antimicrobial therapy for upper respiratory tract infections.
AUTHOR: Guay D R
CORPORATE SOURCE: Institute for the Study of Geriatric Pharmacotherapy, University of Minnesota, College of Pharmacy, and PartneringCare Senior Services, HealthPartners, Minneapolis 55455, USA.. guayx001@tc.umn.edu
SOURCE: CLINICAL THERAPEUTICS, (2000 Jun) 22 (6) 673-84. Ref: 62
Journal code: 7706726. ISSN: 0149-2918.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001128

AB OBJECTIVE: This review examines the issues surrounding short-course antimicrobial therapy of group A beta-hemolytic streptococcal (GABHS) tonsillopharyngitis, acute (suppurative) **otitis media,** and acute sinusitis. BACKGROUND: Accumulating evidence suggests that short-course (ie, < or = 5 days) antimicrobial therapy may have equivalent or superior efficacy compared with traditional longer (10- to 14-day) therapies. RESULTS: In GABHS tonsillopharyngitis, short-course therapy with 6 days of amoxicillin, 4 or 5 days of various cephalosporins, and 5 days of **azithromycin** (10 mg/kg once daily on all 5 days in pediatric patients) are all reasonable alternatives to traditional 10-day

penicillin therapy. In uncomplicated acute (suppurative) **otitis media, single-dose** intramuscular ceftriaxone or 3- to 5-day short-course oral antimicrobial therapy should be effective in > or = 80% of patients. However, more research is needed in children aged <2 years, since short-course therapy may not be successful in most patients in this population. In sinusitis, most short-course therapy data have involved acute maxillary disease in adult patients. Preliminary results are encouraging, but more study is needed, especially in children. CONCLUSIONS: Cost-containment in antimicrobial therapy should include consideration of short-course therapy in the management of upper respiratory tract infections.

L30 ANSWER 7 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:4033 BIOSIS
DOCUMENT NUMBER: PREV200100004033
TITLE: Polymerase chain reaction (PCR) testing of middle ear effusions in pediatric patients with acute **otitis media** (AOM) treated with **single dose azithromycin.**
AUTHOR(S): Ehrlich, G. D. (1); Johnson, S. (1); Hayes, J. (1); Chow, J. H.; Duncanson, F. P.; Dunne, M. W.
CORPORATE SOURCE: (1) Ctr. for Genomic Sciences, Allegheny Univ. of the Health Sciences, Pittsburgh, PA USA
SOURCE: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2000) Vol. 40, pp. 492. print.
Meeting Info.: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy Toronto, Ontario, Canada September 17-20, 2000
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L30 ANSWER 8 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:505931 BIOSIS
DOCUMENT NUMBER: PREV200000505931
TITLE: **Single dose azithromycin** (30 mg/kg) in acute **otitis media.**
AUTHOR(S): Block, Stan L. (1); Arrieta, Antonio; Seibel, Matthew; McLinn, Samuel; Eppes, Stephen C.
CORPORATE SOURCE: (1) Arnold Palmer Hosp for Children and Women, Orlando, FL USA
SOURCE: Clinical Infectious Diseases, (July, 2000) Vol. 31, No. 1, pp. 243. print.
Meeting Info.: 2000 Annual Meeting of the Infectious Diseases Society of America New Orleans, Louisiana, USA September 07-10, 2000
ISSN: 1058-4838.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L30 ANSWER 9 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
ACCESSION NUMBER: 1998:444879 BIOSIS
DOCUMENT NUMBER: PREV199800444879
TITLE: A phase I determination of **azithromycin** in plasma during a 6-week period in normal volunteers after a standard dose of 500mg once daily for 3 days.

AUTHOR(S): Crokaert, F.; Hubloux, A.; Cauchie, P. (1)
CORPORATE SOURCE: (1) Parc Scientifique, Rue du Bosquet 2, 1348 Louvain-la-Neuve Belgium
SOURCE: Clinical Drug Investigation, (Aug., 1998) Vol. 16, No. 2, pp. 161-166.
ISSN: 1173-2563.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Objectives: The pharmacokinetics of **azithromycin** were evaluated in 12 healthy volunteers. Methods: This was an open study in 12 healthy male subjects. Participants received a **single dose** of 2 X 250mg **azithromycin** (two **azithromycin** capsules) administered orally in the fasting state with 240ml water on three consecutive days. Results: After oral intake of two capsules of 250mg **azithromycin** over three consecutive days (the normal treatment regimen in adults), **azithromycin** was present in measurable levels in plasma (>5 mug/L) for 7 to 17 days after the beginning of treatment. The apparent elimination half-life was very long (observed range: 49 to 108 hours, i.e. about 2 to 4.5 days). From the results in plasma, one can extrapolate that the **azithromycin** concentration would remain above 1 mug/L (corresponding to concentrations in tissues above 0.1 mg/L) for up to 15 to 30 days following treatment. The elimination half-life of **azithromycin** (average of 76 hours) was in agreement with values of depletion rates in tissues corresponding to a half-life of 60 to 72 hours. Conclusion: In conclusion, the utility of the long exposure of patients with benign **respiratory infections** to **azithromycin** and to subinhibitory concentrations of **azithromycin** should be questioned.

L30 ANSWER 10 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:90461 BIOSIS
DOCUMENT NUMBER: PREV199900090461
TITLE: **Azithromycin** 3-day course application in treatment of infection of the upper respiratory tract in children.
AUTHOR(S): Andryushchenko, E. V.; Sakharova, A. E.; Bogdanova, A. M.; Kaganov, B. S.
CORPORATE SOURCE: Dep. Child. Dis., I. M. Sechenov Mosc. Med. Acad., B. Pirogovskaya 19, Moscow 119435 Russia
SOURCE: Rossiiskii Vestnik Perinatologii i Pediatrii, (1998) Vol. 43, No. 6, pp. 27-30.
DOCUMENT TYPE: Article
LANGUAGE: Russian
SUMMARY LANGUAGE: Russian; English
AB The analysis of effectiveness and safety of 3-day **azithromycin** course in treatment of infection of upper respiratory tract in 4-14 year-olds was conducted 10 patients had tonsillopharyngitis, 11 - inflammation of the middle ear and 15 - rhinosinusitis. Evaluation of effectiveness and safety of the treatment was done on the basis of the dynamics of the disease clinical features and data of laboratory examination, including clinical blood test and biochemical indexes reflecting function of the liver and kidneys. in 9 patients before therapy the bacteriological examination of ear cavity contents (3 patients), paranasal sinus contents (6 cases) was performed. Prevalently pneumococcal ethiology of infective-inflammatory process in children with otitis and sinusitis was revealed. it was established that after 3-day therapy with **azithromycin** in **single dose** intake per day, the majority of children (97.3%) with infection of upper

respiratory tract had good and satisfactory results of treatment. The tolerance of the medicine was good, side effects were not revealed. The data of the study allow to recommend short **azithromycin** courses as first-line treatment of infection of the upper respiratory tract in pediatric practice.

L30 ANSWER 11 OF 20 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97113990 MEDLINE
DOCUMENT NUMBER: 97113990 PubMed ID: 9124831
TITLE: Comparative study of once-weekly **azithromycin** and once-daily amoxicillin treatments in prevention of recurrent acute **otitis media** in children.
AUTHOR: Marchisio P; Principi N; Sala E; Lanzoni L; Sorella S; Massimini A
CORPORATE SOURCE: Department of Pediatrics (4), University of Milan Medical School, Italy.
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1996 Dec) 40 (12) 2732-6.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 19970506
Entered Medline: 19970424

AB Continuous chemoprophylaxis is effective in the prevention of new episodes of acute **otitis media** (AOM) in otitis-prone children, but compliance can be a problem and thus efficacy can be decreased. Intermittent chemoprophylaxis has so far shown conflicting results. **Azithromycin**, which has a peculiar pharmacokinetics, resulting, even after a **single dose**, in persistently elevated concentrations in respiratory tissues, could permit a periodic administration with higher compliance. We compared a 6-month course of once-weekly **azithromycin** (5 or 10 mg/kg of body weight) with that of once-daily amoxicillin (20 mg/kg) in a single-blind, randomized study of prophylaxis for recurrent AOM in 159 children aged 6 months to 5 years with at least three episodes of AOM in the preceding 6 months. In the amoxicillin group, 23 (31.1%) of 74 children developed 29 episodes of AOM, while in the 10-mg/kg **azithromycin** group, 11 (14.9%) of 74 children experienced 15 episodes. The 5-mg/kg/week **azithromycin** trial was prematurely interrupted after nine cases, due to the high occurrence rate of AOM (55.5%). During the 6-month prophylaxis period, the proportion of children with middle ear effusion declined similarly in both groups. No substantial modification of the nasopharyngeal flora was noted at the end of prophylaxis in both antimicrobial groups. In the 6-month-postprophylaxis follow-up period, about 40% of children in both groups again developed AOM. **Azithromycin** at 10 mg/kg once weekly can be regarded as a valid alternative to once-daily low-dose amoxicillin for the prophylaxis of AOM. Although in the present study no microbiological drawback was noted, accurate selection of children eligible for prophylaxis is mandatory to avoid the risk of emergence of resistant strains.

L30 ANSWER 12 OF 20 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 96415939 MEDLINE
DOCUMENT NUMBER: 96415939 PubMed ID: 8818846
TITLE: Penetration of **azithromycin** into middle ear effusions in acute and secretory **otitis media** in children.
AUTHOR: Pukander J; Rautianen M
CORPORATE SOURCE: Department of Otolaryngology, University of Tampere Medical School, Finland.
SOURCE: JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, (1996 Jun) 37 Suppl C 53-61.
Journal code: 7513617. ISSN: 0305-7453.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19990129
Entered Medline: 19961216

AB In an open-label study, the concentrations of **azithromycin** in middle ear effusions and plasma were determined in 29 children between 1 and 8 years of age with a diagnosis of either secretory **otitis media** of at least 1 month's duration or acute **otitis media**. **Azithromycin** (10 mg/kg) was administered as a **single dose** 12, 24 or 48 h before the insertion of tympanostomy tubes to 17 children with secretory **otitis media** and once daily for 5 days (10 mg/kg on day 1, 5 mg/kg on days 2-5) to 12 children with acute **otitis media**. In the 16 evaluable patients with secretory **otitis media**, **azithromycin** penetrated middle ear effusions, with group mean concentrations approximately two orders of magnitude greater than the concurrent plasma concentrations 12, 24 and 48 h after administration. Similar plasma:effusion ratios were found 24 and 48 h after starting once-daily therapy in 10 evaluable patients with acute **otitis media**.

L30 ANSWER 13 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 7
ACCESSION NUMBER: 96039835 EMBASE
DOCUMENT NUMBER: 1996039835
TITLE: Fundamental and clinical studies on **azithromycin** in obstetrics and gynecology.
AUTHOR: Mikamo H.; Kawazoe K.; Izumi K.; Ito K.; Tamaya T.
CORPORATE SOURCE: Dept. of Obstetrics and Gynecology, School of Medicine, Gifu University, 40, Tsukasa-machi,Gifu city, Gifu 500, Japan
SOURCE: Japanese Journal of Chemotherapy, (1995) 43/SUPPL. 6 (313-318).
ISSN: 1340-7007 CODEN: NKRZE5
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese

AB Fundamental and clinical studies were conducted on **azithromycin** (AZM), a semisynthetic acid stable, macrolide antimicrobial drug, the structure of which is a 15 member lactone ring, in obstetrics and gynecology. The following results were obtained. 1) The MIC90s of AZM against methicillin- susceptible Staphylococcus aureus (MSSA), methicillin-resistant S. aureus (MRSA), Streptococcus agalactiae, **Enterococcus faecalis**, Escherichia coli, Bacteroides fragilis and Prevotella bivia were 0.20, 100, 0.10, 6.25, 25, 12.5 and 6.25 .mu.g/ml, respectively. 2) Concentrations of AZM in the blood and female genital organs after oral administration of 500 mg of AZM were measured. The serum concentrations were 0.45.apprx.0.02 .mu.g/ml at 2.1.apprx.61.2 hours post treatment. The concentrations in the portio vaginalis, cervix uteri, myometrium, endometrium, oviduct and ovary were higher than those in serum; the ranged from 10.8.apprx.0.03 .mu.g/g at 2.1.apprx.61.2 hours posttreatment. 3) Oral administration of 500 mg once a day for 3 days was given to 5 patients with obstetric and gynecological infections (1: endometritis and adnexitis, 4: adnexitis), and 1000 mg as a **single dose** was given to 2 patients with chlamydial cervicitis. The clinical efficacy was excellent in 1 patient and good in 1 with chlamydial cervicitis; good in 4 and poor in 1 with obstetric and gynecological infections. The bacteriological efficacy was eradicated in 2 patients with obstetric and gynecological infections and eradicated in 2 patients with chlamydial cervicitis. There were no adverse reactions or abnormal laboratory findings.

L30 ANSWER 14 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 8
ACCESSION NUMBER: 96039825 EMBASE
DOCUMENT NUMBER: 1996039825
TITLE: Pharmacokinetics of **azithromycin** and its clinical results.
AUTHOR: Aoki N.
CORPORATE SOURCE: Department of Internal Medicine, Shinrakuen Hospital, 1-27 Nishiariake-cho,Niigata 950-21, Japan
SOURCE: Japanese Journal of Chemotherapy, (1995) 43/SUPPL. 6 (234-238).
ISSN: 1340-7007 CODEN: NKRZE5
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
006 Internal Medicine
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese

AB **Azithromycin** (AZM), a new oral azalide antibiotic, was p.o. administered to 5 aged patients with various disturbances of renal function at a **single dose** of 500 mg, to examine its blood concentration and urinary excretion rate. The degree of renal disturbance was graded as mild (Group I) in 1 case, moderate (Group II) in 1 case and severe (Group III) in 3 cases for comparison of the pharmacodynamics in individual groups. As a result, the elimination half-life in blood was revealed to be 45.4 hr in Group I, 30.5 hr in Group II and 29.7 hr in Group III (mean values). The area under the blood concentration time curve (AUC) was 3.83, 4.21 and 4.66 .mu.g .cntdot. h/ml in Groups I, II and III, respectively. The excretion rate in accumulated urine samples of up to 120 hours after administration was 5.57% in Group I, 5.53% in Group II and 4.62% in Group III. AZM was used in 6 patients

with **respiratory infection**, including 1 case of chronic bronchitis, 2 of bronchiectasia+infection and 3 of bronchial asthma +infection. The result was evaluated to he good in all 6 cases. There were no adverse reactions or abnormal laboratory values thought to be due to the drug during the study period. Thus the drug was considered to be a useful agent for treating **respiratory infection**
.

L30 ANSWER 15 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:263327 BIOSIS
DOCUMENT NUMBER: PREV199598277627
TITLE: Efficacy and Tolerability of **Azithromycin** versus Amoxicillin/Clavulanic Acid in Acute Purulent Exacerbation of Chronic Bronchitis.
AUTHOR(S): Beghi, G. (1); Berni, F.; Carratu, L.; Casalini, A.; Consigli, G.; D'Anto, M.; Gioia, V.; Molino, A.; Paizis, G.; Vaghi, A.
CORPORATE SOURCE: (1) Via A. Ponchielli, 10, 26020 Agnadello Italy
SOURCE: Journal of Chemotherapy, (1995) Vol. 7, No. 2, pp. 146-152. ISSN: 1120-009X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB An open randomized trial was conducted in 142 hospitalized and out-patients with acute purulent exacerbation of chronic bronchitis to compare the clinical efficacy and tolerability of **azithromycin** (n = 69) and amoxicillin/clavulanic acid (n = 73). **Azithromycin** (500 mg) was administered as a **single dose** for three days and amoxicillin / clavulanic acid (amoxicillin 875 mg clavulanic acid 125 mg) was given b.i.d. for 8 days (8.16 +/- 1.18). Before therapy and 24-48 hours after the end of treatment, sputum culture (by positioning five orthodontal swabs at the opening of salivary gland ducts after a washing of the oral cavity with sterile saline solution to avoid oral contamination), chest X-rays, arterial blood gas analysis, trials of respiratory functions and routine blood tests were performed. In the **azithromycin** group (69 patients) the efficacy rate was 67.6% (46 patients: 34 cured and 12 improved); in 22 patients (32.4%) the treatment failed; 1 patient was not evaluated because of no follow-up. The overall efficacy rate in the amoxicillin/clavulanic acid group (73 patients) was 97.3% (71 patients: 60 cured and 11 improved); in 1 patient (1.4%) the treatment failed and 1 patient was a drop-out for side effects. All pathogens isolated before treatment were susceptible to the antibiotics administered. At the end of treatment microbiological efficacy was 67.1% in the **azithromycin** group and 98.6% in the amoxicillin/clavulanic acid group. The tolerability was judged good in both treatment groups. Side effects were observed in 1 patient treated with amoxicillin/clavulanic acid (diarrhea), which imposed interruption of treatment, and in 2 patients from the **azithromycin** group (gastralgia and biochemical laboratory tests: renal function). These data suggest that the efficacy of amoxicillin/clavulanic acid in the treatment of bacterial exacerbation of chronic bronchitis is higher than that of **azithromycin**; this new azalide appears to be inadequate for the treatment of this pathology.

L30 ANSWER 16 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 9
ACCESSION NUMBER: 96039810 EMBASE
DOCUMENT NUMBER: 1996039810
TITLE: Therapeutic activity and local delivery of **azithromycin** in animal models of local infection.

AUTHOR: Matsunaga T.; Shimohira H.; Ogawa M.; Sawada Y.; Muto H.; Enogaki K.; Shimooka K.
CORPORATE SOURCE: New Product Development Center, Pfizer Pharmaceuticals Inc., 5-gochi, Taketoyo-cho,Chitagun, Aichi 470-23, Japan
SOURCE: Japanese Journal of Chemotherapy, (1995) 43/SUPPL. 6 (95-99).
ISSN: 1340-7007 CODEN: NKRZE5
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese

AB We compared the therapeutic efficacy of **azithromycin** (AZM), in several localized infection models, with those of clarithromycin (CAM), tosufloxacin (TFLX) and cefaclor (CCL). Local delivery of AZM and CAM to infection sites was also studied. In a rat pouch infection with Staphylococcus aureus, 30 mg/kg doses of AZM at 0, 6 and 24 h post-challenge reduced the CFU by approximately 99% from the initial inoculum. Although the MIC of AZM was 4 and 16 fold higher than that of CAM and TFLX, respectively, AZM demonstrated greater therapeutic efficacy than CAM and TFLX. In a murine model of subcutaneous infection with Streptococcus pyogenes, 25 mg/kg (twice a day) doses of AZM at 1 and 2 days post-challenge produced a 99% reduction of CFU as compared to an untreated control. These effects of AZM were much greater than those of CAM, even though CAM exhibited greater in vitro potency. In a murine **respiratory infection** model with Haemophilus influenzae, a **single dose** of AZM (50 mg/kg) at 4 h post-challenge significantly ($p<0.01$) reduced the CFU as compared with CAM and the untreated control. AZM produced more than 40 times higher concentrations in lungs than in serum, and the lung concentrations exceeded the MIC for the pathogen until at least 48 h post dosing. Lung concentrations of AZM in infected mice were significantly ($p<0.01$) higher than in non infected mice. These results suggest that AZM may have good clinical efficacy in localized human infections because of its high, and prolonged, levels in tissues.

L30 ANSWER 17 OF 20 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 93374682 MEDLINE
DOCUMENT NUMBER: 93374682 PubMed ID: 8396085
TITLE: Comparison of **azithromycin** versus clarithromycin in the treatment of patients with upper respiratory tract infections.
AUTHOR: Muller O
SOURCE: JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, (1993 Jun) 31 Suppl E 137-46.
Journal code: 7513617. ISSN: 0305-7453.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310

ENTRY DATE: Entered STN: 19931022
Last Updated on STN: 19931022
Entered Medline: 19931005

AB The efficacy and safety of **azithromycin** and clarithromycin were compared in an open multicentre study involving 380 adult patients with acute **otitis media**, acute sinusitis, or acute streptococcal pharyngitis or tonsillitis. Patients were assigned randomly to receive **azithromycin** as a **single dose** of 500 mg daily for three days, or clarithromycin 250 mg bid for ten days. Overall clinical efficacy was found to be similar in each treatment group at day 10-14, with a satisfactory outcome (cured or improved) in 95% of **azithromycin** and 96% of clarithromycin patients. Bacteriological efficacy was also similar, with eradication of the pathogen in 94% and 95% of isolates, respectively, in the **azithromycin** and clarithromycin groups. In **otitis media**, a satisfactory clinical response was seen in 97% of patients in each treatment group. **Azithromycin** therapy resulted in a clinical response rate of 93% in sinusitis patients, with bacteriological eradication in 93% of patients. Two patients (who were cured clinically) had persistent pathogens. Similarly, clarithromycin achieved clinical response and bacteriological eradication in 95% and 92% of sinusitis patients, respectively. Pathogens persisted in two patients with clinical cure, and in one case of clinical failure. In pharyngitis or tonsillitis, Streptococcus pyogenes was eradicated successfully in 95% of patients in both groups, and the clinical success rates were 96% and 97% for **azithromycin** and clarithromycin, respectively. No case of clinical failure was associated with persistence of S. pyogenes infection. At the follow-up assessment of this diagnosis group, reinfection had occurred in three (8%) **azithromycin** patients and one (3%) clarithromycin patient, and all but one patient remained asymptomatic. Both drugs were well-tolerated, with 8.4% of patients on **azithromycin** and 7.4% on clarithromycin reporting adverse events, mainly gastrointestinal. It was concluded that a three-day course of **azithromycin** was as effective and well-tolerated as a ten-day course of clarithromycin in adults with acute upper respiratory tract infections.

L30 ANSWER 18 OF 20 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 93374698 MEDLINE
DOCUMENT NUMBER: 93374698 PubMed ID: 8396101
TITLE: Multicentre evaluation of **azithromycin** in comparison with co-amoxiclav for the treatment of acute **otitis media** in children.
AUTHOR: Schaad U B
CORPORATE SOURCE: Department of Paediatrics, University of Bern, Inselspital, Switzerland.
SOURCE: JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, (1993 Jun) 31 Suppl E 81-8.
Journal code: 7513617. ISSN: 0305-7453.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931022
Last Updated on STN: 19980206

Entered Medline: 19931005

AB A total of 389 children (age 0.6-10.2 years) with typical signs and symptoms of acute **otitis media** were randomized (1:1) to treatment with either **azithromycin** or co-amoxiclav. The dosage schedule for **azithromycin** was 10 mg/kg/day, in a single daily dose, administered for three days. Co-amoxiclav was given at a dose of 13.3 mg/kg (amoxycillin equivalent) tid for ten days. Patients were evaluated 4-6 days and 12-16 days after the start of therapy. A satisfactory clinical response was reported for 93.2% of the 192 evaluable **azithromycin**-treated patients (144 cured, 35 improved), and for 97.3% of the 189 evaluable co-amoxiclav-treated patients (148 cured, 36 improved). Six (3.0%) relapses occurred in the **azithromycin** group, and four (2.1%) in the co-amoxiclav treatment group, respectively. Side-effects were recorded in a significantly fewer number of the **azithromycin** patients (23 of 197; 11.7%) compared with the co-amoxiclav patients (43 of 192; 22.4%, $P < 0.02$). Adverse events were mainly gastrointestinal in nature, with diarrhoea the most frequent complaint (32 cases with co-amoxiclav; five with **azithromycin**; $P < 0.001$). One patient from each group discontinued therapy because of treatment-related adverse events. Laboratory analyses (mainly haematological in nature) showed abnormalities in six of 100 **azithromycin** patients and ten of 101 co-amoxiclav patients. It was concluded that three-day, **single-dose azithromycin** and ten-day tid co-amoxiclav therapy have comparable clinical efficacy in paediatric patients with acute **otitis media**; however, there was a lower incidence of side effects in the **azithromycin** group.

L30 ANSWER 19 OF 20 MEDLINE DUPLICATE 12

ACCESSION NUMBER: 93374696 MEDLINE
DOCUMENT NUMBER: 93374696 PubMed ID: 8396099
TITLE: Comparison of **azithromycin** and co-amoxiclav in the treatment of **otitis media** in children.
AUTHOR: Daniel R R
CORPORATE SOURCE: Pfizer Central Research, Sandwich, Kent, UK.
SOURCE: JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, (1993 Jun) 31 Suppl E 65-71.
Journal code: 7513617. ISSN: 0305-7453.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931022
Last Updated on STN: 19980206
Entered Medline: 19931005

AB An open randomized trial was conducted in 159 children (aged 1 to 8 years) with acute **otitis media** to compare the clinical efficacy of **azithromycin** (n = 105) and co-amoxiclav (n = 54). **Azithromycin** (10 mg/kg/day) was administered as a **single dose** for three days and co-amoxiclav was given tid for ten days at a dosage according to the manufacturer's instructions for the country. Of 103 evaluable **azithromycin** patients on day 3 to 5 after the start of therapy, 31 (30%) were considered cured, 67 (65%) improved and

five (5%) failed compared with eight (15%) cured, 45 (83%) improved and one (2%) failed among the 54 evaluable co-amoxiclav treated patients. There was a higher number of **azithromycin** patients with complete resolution of symptoms at this first visit (P = 0.056). By day 10 to 12, clinical equivalence between the two treatment groups was observed with clinical cure in 86 (88%), improvement in 11 (11%) and failure in one (1%) of the 98 **azithromycin** patients, and in the 54 patients treated with co-amoxiclav, clinical cure was observed in 45 (83%), and improvement in nine (17%) patients. Both drugs were well tolerated and treatment related side-effects were reported in 8/105 (8%) **azithromycin** and 2/54 (4%) co-amoxiclav patients. In the **azithromycin** treatment group, these were predominantly mild to moderate gastrointestinal effects, whilst in the co-amoxiclav treatment group, both reports were of mild erythematous rash. One patient from each treatment group was withdrawn due to side-effects (**azithromycin**--diarrhoea and vomiting; co-amoxiclav--erythematous pruritic rash).(ABSTRACT TRUNCATED AT 250 WORDS)

L30 ANSWER 20 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90338465 EMBASE
DOCUMENT NUMBER: 1990338465
TITLE: Antibiotic therapy for common infections.
AUTHOR: Ellison M.J.; Crabtree D.W.
CORPORATE SOURCE: Department of Family Medicine, Family Practice Center, East Carolina University School of Medicine, Greenville, NC 27858-4354, United States
SOURCE: Primary Care - Clinics in Office Practice, (1990) 17/3 (521-541).
ISSN: 0095-4543 CODEN: PRCADR
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Several important points regarding the treatment of urinary tract infections should be made. **Single-dose** and short-course antibiotic therapy is appropriate only for women with acute bacterial cystitis due to E. coli. Studies comparing **single-dose** to full-course therapy have not been sufficiently designed to draw valid statistical conclusions, and only TMP/SMX is recommended at this time. Recurrent UTI in women is almost always due to reinfection, which is best managed by prophylactic antibiotics. Acute bronchitis and acute exacerbations of chronic bronchitis are often due to viral infections, and therefore antibiotic therapy is not always needed. In acute exacerbations of chronic bronchitis, the clearest success rates for antibiotic therapy have been in patients, who have all three of the following symptoms: increased dyspnea, increased sputum production, and sputum purulence. Mupirocin is an important addition to the agents used to treat bacterial skin infections due to streptococcal and staphylococcal strains. In impetigo, mupirocin has been demonstrated to be as effective or superior to oral erythromycin. In prostatitis, data on the fluoroquinolones appears impressive, but further comparative trials are needed. They may become first-line, empiric therapy. The newer oral antibiotics are not recommended as initial, empiric therapy in the outpatient management of common infections, with the possible exception of the treatment of prostatitis. These newer agents may be more important in the treatment of recurrent or resistant infections.

Inventor's work

FILE 'HCAPLUS' ENTERED AT 12:22:07 ON 10 FEB 2003
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L31 8 SEA ABB=ON "DUNNE MICHAEL W"/AU — attached
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L31 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:511111 HCAPLUS
DOCUMENT NUMBER: 133:217317
TITLE: Rationale and design of a secondary prevention trial of antibiotic use in patients after myocardial infarction: The WIZARD (weekly intervention with zithromax [azithromycin] for atherosclerosis and its related disorders) trial
AUTHOR(S): **Dunne, Michael W.**
CORPORATE SOURCE: Pfizer Central Research, Groton, CT, 06340, USA
SOURCE: Journal of Infectious Diseases (2000), 181(Suppl. 3), S572-S578
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mounting evidence supports the contention that atherosclerosis is an inflammatory disease. Recently a possible role for infectious microorganisms has gathered attention. Chlamydia pneumoniae is one possible pathogen. If C. pneumoniae is a target organism, antibiotics with antichlamydial activity may be able to ameliorate plaque instability. The WIZARD trial is a secondary prevention study that is assessing the impact of a 3-mo course of azithromycin compared with placebo on the progression of clin. coronary heart disease. The study will enroll 3300 patients who have had a prior myocardial infarction and who have a C. pneumoniae IgG titer of.gtoreq.1:16. The primary end point is a composite of time to either recurrent myocardial infarction, death, a revascularization procedure, or hospitalization for angina. This study is the first of a series of adequately powered clin. trials that will attempt to bridge insights from preclin. investigations to interventions applicable to patient care.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:784928 HCAPLUS
DOCUMENT NUMBER: 131:346190
TITLE: Azithromycin as treatment for disseminated Mycobacterium avium complex in AIDS patients
AUTHOR(S): Koletar, Susan L.; Berry, Alison J.; Cynamon, Michael H.; Jacobson, Jeffrey; Currier, Judith S.; MacGregor, Rob Roy; **Dunne, Michael W.**; Williams, Debra J.
CORPORATE SOURCE: The Ohio State University Medical Center, Columbus, OH, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1999), 43(12), 2869-2872
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This multicenter, randomized, dose-ranging study was performed to det. the safety and efficacy of two different doses of azithromycin for treating disseminated Mycobacterium avium complex (MAC) in patients with AIDS. Eighty-eight AIDS patients with symptoms and blood cultures consistent with disseminated MAC were treated with 600 or 1,200 mg of azithromycin

daily for 6 wk; 62 patients completed the entire 6 wk of study. Of note, this study was done prior to the time when combination antiretroviral or anti-MAC regimens were the std. of care. Over the 6-wk study period, symptomatic improvement was noted in both dose groups. Microbiol. responses were comparable, with mean decreases of 1.5 and 2.0 log CFU/mL in the high- and low-dose groups, resp. Sterilization of blood cultures occurred in 54% of samples; patients with lower baseline colony counts were more likely to achieve culture negativity. Resistance developed in one patient. Gastrointestinal symptoms were the most common side effects and were more frequent in patients receiving 1,200 mg. Azithromycin is a useful alternative treatment for disseminated MAC infection in AIDS patients. Symptomatic improvement correlates with measurable decreases in mycobacterial load.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:645795 HCAPLUS
DOCUMENT NUMBER: 131:252153
TITLE: Efficacy of azithromycin in prevention of Pneumocystis carinii pneumonia: a randomized trial
AUTHOR(S): **Dunne, Michael W.**; Bozzette, Samuel; McCutchan, J. Allen; Dube, Michael P.; Sattler, Fred R.; Forthal, Donald; Kemper, Carol A.; Havlir, Diane
CORPORATE SOURCE: Pfizer Central Research, Groton, CT, 06340, USA
SOURCE: Lancet (1999), 354(9182), 891-895
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Lancet Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Azithromycin in combination with sulfonamides is active against Pneumocystis carinii pneumonia (PCP) in animals. We assessed the clin. efficacy of azithromycin for PCP prophylaxis in human beings. Methods: We identified HIV-1-infected patients with PCP during a prospective randomized trial comparing azithromycin, rifabutin, and the two drugs in combination for prevention of disseminated Mycobacterium avium infection. Patients had CD4-cell counts less than 100/.mu.L at entry and received PCP prophylaxis according to the std. practice of their clinician. Anal. was by intention to treat. Findings: Patients receiving azithromycin, either alone (n=233) or in combination with rifabutin (n=224), had a 45% lower risk of developing PCP than those receiving rifabutin alone (n=236; p=0.008). Compared with rifabutin alone, hazard ratio for azithromycin was 0.54 (95% CI 0.32-0.94), for azithromycin plus rifabutin was 0.55 (0.32-0.94), and for regimens contg. azithromycin was 0.55 (0.35-0.86). The most common side-effects involved the gastrointestinal tract with dose-limiting toxicities, and were mainly seen in patients receiving combination therapy. Interpretation: Azithromycin as prophylaxis for M avium complex disease provides addnl. protection against P carinii over and above that of std. PCP prophylaxis. Use of azithromycin is beneficial only as primary prophylaxis.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:18769 HCAPLUS
DOCUMENT NUMBER: 130:217651
TITLE: Prophylaxis with weekly versus daily fluconazole for fungal infections in patients with AIDS

AUTHOR(S): Havlir, Diane V.; Dube, Michael P.; McCutchan, J. Allen; Forthal, Donald N.; Kemper, Carol A.; **Dunne, Michael W.**; Parenti, David M.; Kumar, Princy N.; White, A. Clinton, Jr.; Witt, Mallory D.; Nightingale, Stephen D.; Sepkowitz, Kent A.; MacGregor, Rob Roy; Cheeseman, Sarah H.; Torriani, Francesca J.; Zelasky, Michael T.; Sattler, Fred R.; Bozzette, Samuel A.
CORPORATE SOURCE: University of California, San Diego, CA, 92103, USA
SOURCE: Clinical Infectious Diseases (1998), 27(6), 1369-1375
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We compared the efficacy of a 400-mg once-weekly dosage vs. a 200-mg daily dosage of fluconazole for the prevention of deep fungal infections in a multicenter, randomized, double-blind trial of 636 human immunodeficiency virus-infected patients to det. if a less intensive fluconazole regimen could prevent these serious but relatively infrequent complications of AIDS. In the intent-to-treat anal., a deep fungal infection developed in 17 subjects (5.5%) randomly assigned to daily fluconazole treatment and in 24 (7.7%) given weekly fluconazole during 74 wk of follow-up (risk difference, 2.2%; 95% confidence interval [CI], -1.7% to 6.1%). Thrush occurred twice as frequently in the weekly vs. daily fluconazole recipients (hazard ratio, 0.59; 95% CI, 0.40-0.89), and in a subset of patients evaluated, fluconazole resistance was infrequent. Fluconazole administered once weekly is effective in reducing deep fungal infections in patients with AIDS, but this dosage is less effective than the 200-mg-daily dosage in preventing thrush.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:188673 HCAPLUS
DOCUMENT NUMBER: 128:265795
TITLE: Once weekly azithromycin therapy for prevention of Mycobacterium avium complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial
AUTHOR(S): Oldfield, Edward C., III; Fessel, W. Jeffrey; **Dunne, Michael W.**; Dickinson, Gordon; Wallace, Mark R.; Byrne, William; Chung, Raymond; Wagner, Kenneth F.; Paparello, Scott F.; Craig, Daniel B.; Melcher, Gregory; Zajdowicz, Margan; Williams, Richard F.; Kelly, J. William; Zelasky, Michael; Heifets, Leonid B.; Berman, Jonathan D.
CORPORATE SOURCE: Naval Hospital, San Diego, USA
SOURCE: Clinical Infectious Diseases (1998), 26(3), 611-619
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We conducted a randomized, double-blind, placebo-controlled multicenter trial of azithromycin (1,200 mg once weekly) for the prevention of Mycobacterium avium complex (MAC) infection in patients with AIDS and a CD4 cell count of <100/mm3. In an intent-to-treat anal. through the end of therapy plus 30 days, nine (10.6%) of 85 azithromycin recipients and 22 (24.7%) of 89 placebo recipients developed MAC infection (hazard ratio,

0.34; P =.004). There was no difference in the ranges of minimal inhibitory concns. of either clarithromycin or azithromycin for the five breakthrough (first) MAC isolates from the azithromycin group and the 18 breakthrough MAC isolates from the placebo group. Of the 76 patients who died during the study, four (10.5%) of 38 azithromycin recipients and 12 (31.6%) of 38 placebo recipients had a MAC infection followed by death (P =.025). For deaths due to all causes, there was no difference in time to death or no. of deaths between the two groups. Episodes of non-MAC bacterial infection per 100 patient years occurred in 43 azithromycin recipients and 88 placebo recipients (relative risk, 0.49; 95% confidence interval, 0.33-0.73). The most common toxic effect noted during the study was gastrointestinal, reported by 78.9% of azithromycin recipients and 27.5% of placebo recipients. Azithromycin given once weekly is safe and effective in preventing disseminated MAC infection, death due to MAC infection, and respiratory tract infections in patients with AIDS and CD4 cell counts of <100/mm3.

L31 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:635832 HCAPLUS
DOCUMENT NUMBER: 127:287485
TITLE: Azalides: basic and clinical research
AUTHOR(S): **Dunne, Michael W.**
CORPORATE SOURCE: Pfizer Central Research, Groton, CT, USA
SOURCE: Infectious Disease and Therapy (1997), 21(Expanding Indications for the New Macrolides, Azalides, and Streptogramins), 67-73
CODEN: IDTHER; ISSN: 1043-2981
PUBLISHER: Dekker
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 27 refs. on pharmacol. of azalide antibiotics.

L31 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:493613 HCAPLUS
DOCUMENT NUMBER: 127:156102
TITLE: Rationale for the use of azithromycin as Mycobacterium avium chemoprophylaxis
AUTHOR(S): **Dunne, Michael W.**; Foulds, George; Retsema, James A.
CORPORATE SOURCE: Clinical Research Department, Pfizer Central Research, Groton, CT, 06340, USA
SOURCE: American Journal of Medicine (1997), 102(5C), 37-49
CODEN: AJMEAZ; ISSN: 0002-9343
PUBLISHER: Excerpta Medica
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 110 refs., of the microbiol. and pharmacol. aspects of the use of azithromycin for treating M. avium complex disease in HIV-infected patients. It is concluded that azithromycin is a safe, effective, and convenient option for prophylaxis of disseminated M. avium complex disease in such patients.

L31 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:511025 HCAPLUS
DOCUMENT NUMBER: 125:157849
TITLE: Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both

AUTHOR(S): Havlir, Diane V.; Dube, Michael P.; Sattler, Fred R.; Forthal, Donald N.; Kemper, Carol A.; **Dunne, Michael W.**; Parenti, David M.; Lavelle, James P.; White, A. Clinton Jr.; et al.
CORPORATE SOURCE: University California, San Diego, CA, 92103, USA
SOURCE: New England Journal of Medicine (1996), 335(6), 392-398
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Azithromycin is active in treating Mycobacterium avium complex disease, but it has not been evaluated as primary prophylaxis in patients with human immunodeficiency virus (HIV) infection. Because the drug is concd. in macrophages and has a long half-life in tissue, there is a rationale for once-weekly dosing. We compared three prophylactic regimens in a multicenter, double-blind, randomized trial involving 693 HIV-infected patients with fewer than 100 CD4 cells per cubic millimeter. The patients were assigned to receive rifabutin (300 mg daily), azithromycin (1200 mg weekly), or both drugs. They were monitored monthly with blood cultures for M. avium complex. In an intention-to-treat anal., the incidence of disseminated M. avium complex infection at one year was 15.3 percent with rifabutin, 7.6 percent with azithromycin, and 2.8 percent with both drugs. The risk of the infection in the azithromycin group was half that in the rifabutin group (hazard ratio, 0.53; P=0.008). The risk was even lower when two-drug prophylaxis was compared with rifabutin alone (hazard ratio, 0.28; P<0.001) or azithromycin alone (hazard ratio, 0.53; P=0.03). Among the patients in whom azithromycin prophylaxis was not successful, 11 percent of M. avium complex isolates were resistant to azithromycin. Dose-limiting toxic effects were more common with the two-drug combination than with azithromycin alone (hazard ratio, 1.67; P=0.03). Survival was similar in all three groups. For protection against disseminated M. avium complex infection, once-weekly azithromycin is more effective than daily rifabutin and infrequently selects for resistant isolates. Rifabutin plus azithromycin is even more effective but is not as well tolerated.

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SnJ 10430643

FDA Briefing Package:
Zithromax® (Azithromycin) Oral Suspension
Single-Dose and Three-Day Treatment of Acute Otitis Media

Anti-Infective Drugs Advisory Committee
November 7, 2001

Table of Contents

List of Abbreviations

AE – Adverse Event

Amox/Clav – Amoxicillin and Clavulanic Acid

AOM – Acute Otitis Media

$AUC_{0-\infty}$ – Area under the Serum Concentration-Time Curve

AUC_{0-24} – Area under the Serum Concentration-Time Curve for 24 Hours

Azi – Azithromycin

CFTX – Ceftriaxone

EOT – End-of-Therapy Visit

IM –.Intramuscular

MIC – Minimum Inhibitory Concentration

MITT – Modified Intent-to-Treat Population

TM – Tympanic Membrane

TOC – Test-of-Cure Visit

Glossary of Terms

The following definitions are provided as terms that identify consistent features of particular study designs used in AOM trials. These terms will be used in this briefing package and during the advisory committee meeting for consistency and for ease of reference to particular designs.

Clinical-Only Study – A comparative study of antibiotics for the treatment of AOM that does not include the use of tympanocentesis. Subjects are enrolled in the study based on the presence of clinical signs and symptoms of AOM. Outcome is based on resolution or improvement of clinical signs and symptoms at time points following completion of antimicrobial treatment. The objective of this study is to demonstrate similar clinical outcomes for a test drug and comparator at a defined time point.

Microbiologic studies include tympanocentesis for isolation of bacterial pathogens from middle ear fluid. These studies fall into two categories:

Single-Tap Study – A study, often non-comparative, in which tympanocentesis is performed at study entry. Subjects are enrolled based on clinical signs and symptoms, and tympanocentesis is performed to identify patients with bacterial pathogens. Outcome is based on resolution or improvement of clinical signs and symptoms at time points following completion of antibiotic treatment, similar to clinical only studies. The objective of the study is to demonstrate favorable clinical outcomes in subjects with pathogens identified by tympanocentesis at study entry.

Double-Tap Study – A study in which tympanocentesis is performed at study entry and during therapy. Subjects are enrolled based on clinical signs and symptoms, and tympanocentesis is performed to identify patients with bacterial pathogens. Outcome is based on eradication of pathogens from a second tympanocentesis performed within a few days (typically 3-6) after study entry. Clinical outcome at later visits may also be assessed. The objective of the study is to demonstrate favorable rates of bacterial eradication in subjects with pathogens identified by tympanocentesis at study entry.

Background

Zithromax® (azithromycin) has been approved in the United States with a 5-day dosing regimen for the treatment of a number of infectious diseases, including acute exacerbation of chronic bronchitis, pharyngitis/tonsillitis, community-acquired pneumonia, and uncomplicated skin and skin structure infections in adults, as well as acute otitis media and pharyngitis/tonsillitis in children. In adults, the recommended total dose of azithromycin administered over 5 days is 1,500 mg (500 mg on day 1 and 250 mg on days 2-5). In children, the recommended total dose of azithromycin administered over the 5 days is 30 mg/kg (10mg/kg on day 1 and 5 mg/kg on days 2-5) to treat acute otitis media. This will be referred to as the five-day regimen throughout this document. These approvals were based on data demonstrating the safety and effectiveness of azithromycin compared with standard regimens approved for the treatment of these conditions. The studies supporting use of this five-day regimen for treatment of AOM are described in the clinical studies section of the label for Zithromax® oral suspension. Excerpted information from the label is provided as Reference 1.

The application under review seeks to shorten the duration of treatment for AOM. The same total dose of azithromycin (30 mg/kg) given in the five-day regimen is proposed to be given in one or three days. In the one-day treatment regimen, a single dose of 30 mg/kg of azithromycin is given. The three-day treatment regimen gives 10 mg/kg of azithromycin once daily for three days. Pfizer, Inc. has submitted the following pivotal studies for approval of the one-day and three-day treatment regimens.

Pivotal Studies for this Application

Otitis Media Studies	Design	Azi Dose	Azi Duration	Comparators
A0661014	Clinical-Only, Double-Blind	10 mg/kg	3 days	Amox/Clav (Augmentin®)
R-0581	Clinical-Only, Double-Blind	30 mg/kg	Single Dose	Amox/clav
A0661015	Single-Tap, Open-label	30 mg/kg	Single Dose	None

Additional supportive evidence from a single-tap study (AZM-NY-95-001) performed at a single center in Costa Rica was submitted. This study compared the one-day and three-day regimens to ceftriaxone for treatment of AOM.

Microbiology

The class of antimicrobials known as the macrolides includes azithromycin, erythromycin, clarithromycin, and dirithromycin. Azithromycin is a member of the azalide subclass of macrolides and is proposed for treatment of acute otitis media caused by *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae.* The microbiological information of interest is the spectrum of azithromycin versus these potential pathogens, and the mechanisms of resistance mediated by these pathogens that may affect efficacy.

In vitro spectrum of activity

The table on the following page provides a brief summary representing the in vitro susceptibility of *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae* to azithromycin. The *S. pneumoniae* susceptibility profile represents isolates from U. S. medical centers from 1996-1997 and 1999-2000. These and other surveillance studies suggest that susceptibility and resistance profiles for these agents of the macrolide class are virtually identical to each other and justify the use of erythromycin susceptibility testing for other members of this class. These surveillance studies, performed at sequential intervals of time, also show that macrolide, and thus azithromycin resistance is increasing, especially in the penicillin intermediate and resistant strains. Surveillance studies also demonstrate that erythromycin resistant rates vary from 6.1% to 53.7% in participating medical centers and that approximately 25% of the *S. pneumoniae* are resistant to macrolides.[1]

At least 8 U. S. surveillance studies for *Haemophilus influenzae* and 4 for *Moraxella catarrhalis* have been performed in the last 15 years. The results of current studies of community acquired respiratory tract isolates[3] and isolates from outpatient clinics[4] are presented in Table 1 and clearly show that greater than 90 percent of the isolates examined remain susceptible to azithromycin at the current breakpoint. Less than 0.3 percent of the *Haemophilus influenzae* isolates have been shown to be resistant to azithromycin.

Mechanisms of Action

Azithromycin acts by binding reversibly to the 23S rRNA component of the 50S ribosomal subunit of susceptible microorganisms, thereby blocking the translocation reaction of polypeptide chain elongation.

Mechanisms of Resistance

Point mutation or modification (methylation) of the target site resulting in reduced affinity of the drug to the target mediates resistance to macrolides in clinical pathogens. Resistance is also mediated by decreased permeability (efflux) resulting in decreased drug concentration. Finally, it may be due to modification of the antimicrobial (esterases, acetyltransferase, and phosphotransferase) resulting in inactivation of the macrolide. Of these resistant mechanisms, modification of the target site, 23S ribosomal RNA, by

methylation (erythromycin resistance methylase, *erm*) and efflux (*mef(A)*) are found in the pathogens of interest.

The two predominant macrolide resistance mechanisms in *S. pneumoniae* are expression of the *mef(A)* and *erm*(B) genes. In the U.S. the predominant resistant determinant appears to be *mef(A)*, accounting for ~66.5% macrolide resistance. Generally, strains with *mef(A)* have erythromycin (EM) MICs of 1-32 μg/mL and clindamycin (CM) MICs $\leq$0.125 μg/mL. Strains with *erm*(B) determinants usually have EM MICs $\geq$64 μg/mL and CM MICs $\geq$8.0 μg/mL.

Some *Haemophilus influenzae* and other gram-negative species have innate resistance to macrolides, thought to be mediated by the broad specificity efflux pump AcrAB-TolC. As seen from Table 1, the *Haemophilus influenzae* MIC_{90} is 2.0 μg/mL and shows that a majority of the strains are below the susceptible breakpoint of 4 μg/mL.

Azithromycin in vitro spectrum of activity for select pathogens

Pathogen	# strains	MIC range	MIC_{50}	MIC_{90}	Ref
S. pneumoniae	1531	≤0.03 - >64	0.12	16.0	1
PEN ^{S}	1008	≤0.03 - >64	0.12	0.25	
PEN ^{I}	194	≤0.03 - >64	0.25	>64	
PEN ^{R}	329	≤0.06 - >64	8.0	>64	
EM	1531	≤0.06 - >64	0.06	8.0	
S. pneumoniae	----	----	----	----	2
PEN ^{S}	2849	≤0.125 - ≥64	≤0.125	≤0.125	
PEN ^{I}	1059	≤0.125 - ≥64	≤0.125	4.0	
PEN ^{R}	581	≤0.125 - ≥64	1.0	≥64	
H. influenzae	1077	≤0.125 - >16	2.0	2.0	3
	1032	0.03 - 16	1.0	2.0	4
M. catarrhalis	503	≤0.125 - 0.25	≤0.125	≤0.125	3
	444	≤0.03 - >64	0.06	0.12	4

[1] Doren, G. V., K.P. Heilmann, H.K. Huynh, et.al. 2001. Antimicrobial Resistance among Clinical Isolates of *Streptococcus pneumoniae* in the United States during 1999-2000, Including a Comparison of Resistant Rates since 1994-1995. Antimicrob. Agents Chemother. 45:1721-1729.

[2] Mason, E.O. Jr., L.B. Lamberth, N.L. Kershaw, et.al. 2000. *Streptococcus pneumoniae* in the USA: In vitro susceptibility and pharmacodynamic analysis. J. Antimicrob. Chemother. 45:623-631.

[3] Doren, G.V., R.N. Jones, M. A. Pfaller, et.al. 1999. *Haemophilus influenzae* and *Moraxella catarrhalis* from patients with Community-Acquired Respiratory Tract Infections: Antimicrobial Susceptibility Patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada 1997). Antimicrob. Agents Chemother. 43:385-389.

[4] Thornsberry, C., P.T. Ogilvie, H. P. Holley, et. al. 1999. Survey of Susceptibility of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* Isolates to 26 Antimicrobial Agents: A Prospective U.S. Study. Antimicrob. Agents Chemother. 43:2612-2623.

Clinical Pharmacology and Biopharmaceutics

The pharmacokinetic parameter that appears to be most predictive of azithromycin efficacy is the ratio of the area under the serum concentration-time curve ($AUC_{0-\infty}$) to the organism's minimal inhibitory concentration (MIC), the $AUC_{0-\infty}$/MIC ratio. The concept of accelerated dosing assumes that the pharmacokinetics of azithromycin are linear across the proposed dosing range, resulting in a similar exposure ($AUC_{0-\infty}$) and $AUC_{0-\infty}$/MIC by administering the same total dose.

Pharmacokinetics in pediatric subjects:

The pharmacokinetics of azithromycin following the administration of 20 mg/kg/day × 3 days, 12 mg/kg/day × 5 days, and 10 mg/kg/day × 3 days were evaluated in pediatric subjects with pharyngitis/tonsillitis or other bacterial infections. The studies were non-comparative and the 1-day regimen (30 mg/kg) was not evaluated. Blood samples were collected for only 24 hours following the last dose. Thus, the area under the serum concentration-time curve for 24 hrs (AUC_{0-24}) following the last dose is the only measure of exposure that can be assessed. The AUC_{0-24} following the last dose were 3.93, 7.92, and 2.35 μg*hr/mL for 20 mg/kg/day, 12 mg/kg/day, and 10 mg/kg/day, respectively. Since the half-life of azithromycin is approximately 68 hours, accumulation is still occurring at day 3 and day 5. After correction for the administered dose, the results demonstrate that the exposure from the 3-day regimen ranged from 28% less to 21% greater than the 5-day regimen. Although the AUC_{0-24} is similar among the regimens, the reviewer is unable to conclude that the overall exposure ($AUC_{0-\infty}$) from 3-day and 5-day regimens is similar since the studies were not designed to provide this information.

Pharmacokinetics in adult subjects (3-day vs. 5-day):

The pharmacokinetics of azithromycin following the administration of 500 mg/day × 3 days vs. 500 mg on day 1 followed by 250 mg × 4 days were evaluated in three comparative studies with healthy adult subjects (066-087, AZM-NY-90-011, and AZM-F-93-004). The data from AZM-NY-90-011 were excluded from the analysis since the accuracy of the analytical methods was outside of the ±15% acceptable range. Limited blood samples were obtained from study 066-087, excluding the first and last dosing interval, and introduced uncertainty in the results from the non-parametric analysis. Thus, the raw data from study 066-087 were fit to a 3-compartment, oral absorption model using Win Nonlin (version 3.1). The $AUC_{0-\infty}$ from the 3-day regimen was compared to the 5-day regimen of each study using a geometric mean ratio (GMR, 3-day/5-day) and 90% confidence interval. The GMR (90% confidence interval) for study AZM-F-93-004 was 0.933 (0.798 to 1.092). Thus, the $AUC_{0-\infty}$ from the 3-day and 5-day regimens was similar. The GMR for study 066-087 using observed and simulated concentrations was 1.185 and 1.118, respectively. The 90% confidence interval exceeded 1.25 in both instances. The two studies support that the $AUC_{0-\infty}$ associated with a 3-day regimen is similar to a 5-day regimen.

Pharmacokinetics in adult subjects (1-day vs. 3-day):
The pharmacokinetics of azithromycin following the administration of 1,500 mg as a single dose vs. 500 mg/day × 3 days were evaluated in a comparative study with healthy adult subjects (GA2000). The analytical methods in this study had a lower limit of quantitation (LLOQ) approximately 5-fold greater than previous studies, resulting in azithromycin concentrations below the LLOQ within 48 hours in the majority subjects following a single dose and by the end of each dosing interval in most subjects for the 3-day regimen. Using the data provided, the $AUC_{0-\infty}$ GMR (90% confidence interval) was 1.235 (0.935 to 1.632) and the sponsor concluded that the exposure from the two regimens was similar. However, the sponsor used azithromycin concentrations below the LLOQ to estimate the terminal elimination rate constant and $AUC_{0-\infty}$ in both regimens. The reviewer estimated the AUC_{0-t} using concentrations above the LLOQ. The AUC_{0-t} GMR was 0.829 but included data from only five subjects. Since the exposure from the 1-day regimen may be less than the 3-day regimen, the reviewer is unable to state that the overall exposure is similar between the two regimens.

Pharmacokinetics in adult subjects (1-day vs. 5-day):
The sponsor did not conduct a study comparing the $AUC_{0-\infty}$ resulting from 1,500 mg as a single dose vs. 500 mg on day 1 followed by 250 mg/day × 4 days.

Study A0661014: Clinical-Only Study of Azi Three-Day Treatment vs. Amox/Clav for AOM

Study A0661014 was a double-blind, multicenter, randomized trial comparing 10 mg/kg daily dose of azithromycin for 3 days with a ten-day course of amox/clav (45 mg/kg/day given BID) in the treatment of AOM in children ages 6 months to 12 years. This was a clinical-only study with enrollment of 373 patients from 28 U. S. study sites.

The following table shows the clinical outcomes for the MITT and per protocol populations as reported by the applicant. Outcomes are reported for end of therapy (Study day 8 to 12) and test of cure (Study day 20 to 32) visits.

Study A0661014: Clinical Outcomes

	Azithromycin		Amox/Clav		95% Confidence Interval of Difference
	N	(%)	N	(%)	
MITT Population					
Patients evaluable at EOT	185	(100)	181	(100)	
Success (Cured or Improved)	153	(83)	159	(88)	-12.9, 2.7
Failure	32	(17)	22	(12)	
Patients evaluable at TOC	182	(100)	180	(100)	
Cure	134	(74)	124	(69)	- 5.2, 14.6
Failure	48	(26)	56	(31)	
Per Protocol Population					
Patients evaluable at EOT	166	(100)	151	(100)	
Success (Cured or Improved)	134	(81)	129	(85)	-13.6, 4.2
Failure	32	(19)	22	(15)	
Patients evaluable at TOC	179	(100)	175	(100)	
Cure	131	(73)	120	(69)	- 5.4, 14.7
Failure	48	(27)	55	(31)	
EOT = Day 8 – 12; TOC = Day 20 – 32					

The results of this clinical study support the conclusion that 10 mg/kg/day for 3 days of azithromycin has similar effectiveness to a ten-day course of amoxicillin/clavulanate in the treatment of AOM. The end of therapy and test of cure analyses of the per protocol population support those of the MITT population.

In this study, 114 (31%) of the treated patients were 1 month to 2 years of age, and 259 (69%) were >2 years of age. The following table shows the clinical outcomes by age for the MITT population.

Study A0661014: Clinical Outcomes by Age (MITT Population)

	Azithromycin N	(%)	Amox/Clav N	(%)	95% Confidence Interval of Difference
Age ≤2 years					
Patients evaluable at EOT	60	(100)	52	(100)	
Success (Cured or Improved)	45	(75)	44	(85)	-26.2, 7.0
Failure	15	(25)	8	(15)	
Patients evaluable at TOC	58	(100)	52	(100)	
Cure	35	(60)	30	(58)	-17.7, 23.1
Failure	23	(40)	22	(42)	
Age >2 years					
Patients evaluable at EOT	127	(100)	129	(100)	
Success (Cured or Improved)	108	(85)	115	(89)	-13.1, 4.9
Failure	19	(15)	14	(11)	
Patients evaluable at TOC	124	(100)	128	(100)	
Cure	99	(80)	94	(73)	-4.8, 17.6
Failure	25	(20)	34	(27)	
EOT = Day 8 – 12; TOC = Day 20 –32					

When outcomes were evaluated by patient age ≤ 2 years or > 2 years, response rates between the treatment groups were similar. For both drugs, children > 2 years were more likely to have a successful clinical response than were children ≤ 2 years.

This clinical-only study of AOM includes an unknown proportion of patients with sterile middle ear fluid. The results reported here must be correlated with those from microbiologic studies using diagnostic tympanocenteses.

AOM has a high spontaneous resolution rate, and the effect of antimicrobial treatment is limited. Because there was no placebo group in this study, the true effect of the study drugs is unknown.

Study R-0581: Clinical-Only Study of Azi One-Day Treatment vs. Amox/Clav for AOM

Study R-0581 was a double-blind, double-dummy, multicenter, randomized trial comparing a single 30 mg/kg dose of azithromycin with a ten day course of amoxicillin/clavulanate (45 mg/kg/day given BID) in the treatment of acute otitis media (AOM) in children 6 months to 12 years of age. This was a clinical-only study with enrollment of 350 patients (175 azithromycin, 175 amoxicillin/clavulanate) from nine U.S. study sites.

The following table shows the clinical outcomes for the modified intent-to-treat (MITT) and per protocol populations as reported by the applicant. Outcomes are reported for end of therapy (Study day 12 to 16) and test of cure (Study day 28 to 32) visits.

Study R-0581: Clinical Outcomes

	Azithromycin N	(%)	Amox/Clav N	(%)	95% Confidence Interval of Difference
MITT Population					
Patients evaluable at EOT	160	(100)	161	(100)	
Success (Cured or Improved)	139	(87)	142	(88)	-9.2, 6.5
Failure	21	(13)	19	(12)	
Patients evaluable at TOC	151	(100)	154	(100)	
Cure	114	(75)	116	(75)	-10.2, 10.5
Failure	37	(25)	38	(25)	
Per Protocol Population					
Patients evaluable at EOT	147	(100)	148	(100)	
Success (Cured or Improved)	127	(86)	129	(87)	-9.2, 7.7
Failure	20	(14)	19	(13)	
Patients evaluable at TOC	144	(100)	142	(100)	
Cure	107	(74)	107	(75)	-11.8, 9.7
Failure	37	(26)	35	(25)	

EOT = End of Therapy (Day 12 to 16); TOC = Test of Cure (Day 28 to 32)

The results of this clinical study support the conclusion that a single 30 mg/kg dose of azithromycin has similar effectiveness to a ten day course of amoxicillin/clavulanate in the treatment of AOM. The end of therapy and test of cure analyses of the per protocol population support those of the MITT population.

In this study, 138 (40%) of the treated patients were ≤ 2 years of age, and 208 (60%) were > 2 years of age. The following table shows the clinical outcomes by age for the MITT population.

Study R-0581: Clinical Outcomes by Age (MITT Population)

	Azithromycin		Amox/Clav		95% Confidence
	N	(%)	N	(%)	Interval of Difference
Age ≤ 2 Years					
Patients evaluable at EOT	68	(100)	56	(100)	
Success (Cured or Improved)	53	(78)	45	(80)	-18, 13.7
Failure	15	(22)	11	(20)	
Patients evaluable at TOC	64	(100)	53	(100)	
Cure	41	(64)	30	(57)	-12.2, 27.1
Failure	23	(36)	23	(43)	
Age > 2 Years					
Patients evaluable at EOT	92	(100)	105	(100)	
Success (Cured or Improved)	86	(93)	97	(92)	-7.1, 9.3
Failure	6	(7)	8	(8)	
Patients evaluable at TOC	87	(100)	101	(100)	
Cure	73	(84)	86	(85)	-12.7, 10.3
Failure	14	(16)	15	(15)	
EOT=End of Therapy (Day 12 to 16); TOC=Test of Cure (Day 28 to 32)					

When outcomes were evaluated by patient age ≤ 2 years or > 2 years, response rates between the treatment groups were similar. For both drugs, children > 2 years were more likely to have a successful clinical response than were children ≤ 2 years.

The same caveats noted with study A0661014 apply to this study. These include the enrollment of patients with sterile middle ear fluid, the need for correlation with microbiologic studies, the high spontaneous resolution rate, and inability to compare outcomes directly to placebo treatment.

Study A0661015: Single-Tap Study of Azi One-Day Treatment for AOM

Study A0661015 was an open-label, non-comparative, multi-center trial of AOM using a single 30 mg/kg dose of azithromycin in children 6 months to 12 years of age. The study design included tympanocentesis performed at baseline to identify patients with bacterial AOM. Outcomes are based on clinical assessments at specified time points. This study enrolled 248 patients from 22 U. S. and Latin American study sites.

The following table shows the clinical outcomes for the MITT and per protocol populations as reported by the applicant. Outcomes are reported for EOT (Study day 8 to 12) and TOC (Study day 20 to 32) visits.

Study A0661015: Clinical Outcomes

	Azithromycin N	(%)	95% Confidence Interval of Point Estimate
MITT Population			
Patients evaluable at EOT	240	(100)	
Success (Cured or Improved)	213	(89)	84.5, 93.0
Failure	27	(11)	
Patients evaluable at TOC	242	(100)	
Cure	206	(85)	80.4, 89.8
Failure	39	(15)	
Per Protocol Population			
Patients evaluable at EOT	215	(100)	
Success (Cured or Improved)	190	(88)	83.9, 92.9
Failure	25	(12)	
Patients evaluable at TOC	229	(100)	
Cure	195	(85)	80.3, 90.0
Failure	34	(15)	
EOT = Day 8 to 12; TOC = Day 20 to 32			

Clinical outcomes in MITT patients with a pathogen identified at the baseline visit are shown in the following table.

Study A0661015: Clinical Outcome by Baseline Pathogen (MITT Population)

EOT Assessment:	***H. influenzae* (N=42)**		***M. catarrhalis* (N=10)**		***S. pneumoniae* (N=76)**	
Outcome	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Success	30 (71%)	56.6, 86.3	10 (100%)	95.0, 100	70 (92%)	85.4, 98.8
Cure	18 (43%)		5 (50%)		49 (64%)	
Improvement	12 (29%)		5 (50%)		21 (28%)	
Failure	12 (29%)		0 (0%)		6 (8%)	
TOC Assessment:	***H. influenzae* (N=44)**		***M. catarrhalis* (N=10)**		***S. pneumoniae* (N=76)**	
Outcome	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Cure	28 (64%)	48.3, 79.0	10 (100%)	95.0, 100	67 (88%)	80.2, 96.1
Failure	16 (36%)		0 (0%)		9 (12%)	

Of particular note, 12 of 76 (16%) *S. pneumoniae* isolates were resistant to azithromycin. The clinical success rates at EOT and TOC were 10/12 and 8/12, respectively.

This Single-Tap study demonstrates clinical cure rates at EOT roughly similar to those for azithromycin-treated patients in the "Clinical Only" studies. However, the success rates for patients with *H. influenzae* identified by baseline tympanocentesis are lower than for the overall population. These lower cure rates for patients with *H. influenzae* at baseline are similar to cure rates for patients treated with the approved regimen of azithromycin.

In this study, 86 (35%) of the treated patients were ≤2 years of age, and 162 (65%) were >2 years of age. The following table shows clinical outcomes by age for the MITT population.

Study A0661015: Clinical Outcomes by Age (MITT Population)

	Azithromycin N	(%)	95% Confidence Interval of Point Estimate
Age ≤2 years			
Patients evaluable at EOT	82	(100)	
Success (Cured or Improved)	69	(84)	75.6, 92.7
Failure	13	(16)	
Patients evaluable at TOC	83	(100)	
Cure	64	(77)	67.5, 86.7
Failure	19	(23)	
Age >2 years			
Patients evaluable at EOT	158	(100)	
Success (Cured or Improved)	144	(91)	86.4, 95.9
Failure	14	(9)	
Patients evaluable at TOC	159	(100)	
Cure	142	(89)	84.2, 94.4
Failure	17	(11)	
EOT = End of Therapy (Day 8 to 12); TOC = Test of Cure (Day 20 to 32)			

Children > 2 years of age were more likely to have a successful clinical response than were children ≤2 years. Similar results are seen when patients with a baseline pathogen are grouped by age, as shown in the following table.

Study A0661015: Clinical Outcome by Baseline Pathogen and Age (MITT Population)

	H. influenzae		*S. pneumoniae*	
EOT Assessment:	**≤2 years**	**>2 years**	**≤2 years**	**>2 years**
Outcome	N (%)	N (%)	N (%)	N (%)
Success	11 (61%)	19 (79%)	23 (92%)	47 (92%)
Failure	7 (39%)	5 (21%)	2 (8%)	4 (8%)
TOC Assessment:				
Outcome	N (%)	N (%)	N (%)	N (%)
Cure	10 (53%)	18 (72%)	20 (80%)	47 (92%)
Failure	9 (47%)	7 (28%)	5 (20%)	4 (8%)

Study AZM-NY-95-001: Supportive Single-Tap Study of One-Day Azi vs. Three-Day Azi vs. IM Ceftriaxone

Study AZM-NY-95-001 was a single center (Costa Rica) trial of AOM comparing a single 30 mg/kg dose of azithromycin, 10 mg/kg daily of azithromycin for 3 days, and 50 mg/kg of IM CFTX. Initially, the study used a double-dummy, double-blind design, but due to the color of reconstituted CFTX the injection was unblinded. The investigator remained blinded to the dose regimen of azithromycin. This was a single-tap study with outcome assessments at EOT (days 9 to 19) and follow-up (days 26 to 44). One hundred ninety-eight subjects (66 azi single dose; 66 azi 3-day; 66 CFTX) were randomized to treatment. Ninety-eight subjects (30 azi single dose; 35 azi 3-day; and 33 CFTX) had an appropriate pathogen isolated at baseline, and were included in the evaluation of clinical response by baseline pathogen.

Clinical success (cure or improvement) was reported for 93.8% of azi single dose, 92.4% of azi 3-day, and 96.9% of CFTX patients at the follow-up visit.

Clinical outcomes in MITT patients with *H. influenzae* or *S. pneumoniae* at the baseline visit are shown in the following table. There were only two patients with *M. catarrhalis* enrolled in the study. Both patients were treated with the 3-day regimen of azithromycin and both were clinical cures.

Study AZM-NY-95-001: Clinical Outcome by Baseline Pathogen (MITT Population)

EOT Assessment:	***H. influenzae***			***S. pneumoniae***		
Outcome	1-Day Azi N (%)	3-Day Azi N (%)	CFTX N (%)	1-Day Azi N (%)	3-Day Azi N (%)	CFTX N (%)
Total Patients	9 (100%)	15 (100%)	10 (100%)	21 (100%)	18 (100%)	23 (100%)
Success	8 (89%)	14 (93%)	10 (100%)	20 (95%)	15 (83%)	23 (100%)
Failure	1 (11%)	1 (7%)	0	0	0	0
Missing	0	0	0	1 (5%)	3 (17%)	0
TOC Assessment:	***H. influenzae***			***S. pneumoniae***		
Outcome	1-Day Azi N (%)	3-Day Azi N (%)	CFTX N (%)	1-Day Azi N (%)	3-Day Azi N (%)	CFTX N (%)
Total	9 (100%)	15 (100%)	10 (100%)	21 (100%)	18 (100%)	23 (100%)
Cure	7 (78%)	11 (74%)	9 (90%)	20 (95%)	17 (94%)	23 (100%)
Failure	1 (11%)	2 (13%)	0	0	0	0
Missing	1 (11%)	2 (13%)	1 (10%)	1 (5%)	1 (6%)	0

Efficacy

The descriptions of the individual clinical studies summarize the outcome information supplied by the applicant in support of the one-day and three-day dosage regimens for treatment of acute otitis media. The clinical studies section of the label for the Zithromax® oral suspension (Ref. #1) summarizes the information provided in support of the five-day regimen.

The clinical-only study of the five-day treatment regimen showed clinical outcomes at EOT of 88% for azi and the control agent. Clinical outcomes at TOC were 73% for azi and 71% for the comparator. The clinical-only study for the three-day regimen (study A0661014) showed MITT cure rates of 83% for azi and 88% for amox/clav at EOT. At TOC, the cure rates were 74% for azi and 69% for amox/clav. The clinical-only study for the one-day regimen (study R-0581) showed MITT cure rates of 87% for azi and 88% for amox/clav at EOT. At TOC, the cure rates were 75% in both treatment arms.

The clinical outcomes for patients with *S. pneumoniae* and *H. influenzae* at EOT and TOC for the different treatment regimens are summarized in the following table.

Dose Groups	30 mg/kg – SD (One-Day)	10 mg/kg x 3 (Three-Day)	10 mg/kg – Day 1 5 mg/kg – Days 2-5 (Five-Day)	Comparator
EOT Assessment				
H. influenzae	38/51 (74%)	14/15 (93%)	52/65 (80%)	19/19 (100%)
S. pneumoniae	90/97 (92%)	15/18 (83%)	86/103 (84%)	39/39 (100%)
TOC Assessment				
H. influenzae	35/53 (66%)	11/15 (74%)	38/57 (67%)	15/18 (83%)
S. pneumoniae	87/97 (90%)	17/18 (94%)	62/84 (74%)	41/45 (91%)

In a review of the published literature, there was additional information regarding clinical and microbiologic efficacy from two comparative double-tap studies conducted by Dagan et al. Of particular note are the relatively low bacterial eradication rates for patients with *H. influenzae* treated with azithromycin in both of these studies. The articles, References 2 and 3, are provided in this package for your review.

Safety

Number of Subjects Treated
Phase 2-4 Studies

As of the June 30, 2000 cutoff date, 2590 subjects received azithromycin in the Phase 2-4 pooled studies. A total of 1897 subjects received other antibiotics in the comparative trials. The number of subjects receiving azithromycin and the individual comparative agents in the U. S./Canada and outside North America in the pooled Phase 2-4 studies is provided below.

	Number of Subjects Treated		
Treatment	**U.S./Canadian**	**Non-North American**	**Total**
Azithromycin	518	2072	2590
Amox/Clav	358	423	781
Penicillin V	0	394	394
Cefaclor	0	315	315
Clarithromycin	0	307	307
Erythromycin	0	19	19
CFTX	0	66	66
Cefixime	0	15	15
TOTAL	876	3611	4487

Adverse Events

A summary of the most common treatment-related adverse events is presented below for subjects who received azithromycin or a comparator in Phase 2-4 studies. Information on the five-day dose regimen is from the original NDA application. Caution should be taken in making comparisons between the five-day regimen and the shorter duration regimens. Caution should also be taken in making comparisons with all comparator patients, since patients who participated in studies of pharyngitis are included in this group. For instance, part of the reason for a higher frequency of headache in the comparator is likely related to the expected occurrence of that AE in pharyngitis patients.

Commonly Reported Treatment-Related Adverse Events (≥5 Subjects in Either Azithromycin or Comparator Group)

Dose Groups	**30 mg/kg – SD (One-Day)**	**10 mg/kg x 3 (Three-Day)**	**10 mg/kg – Day 1 5 mg/kg – Days 2-5 (Five-Day)**	**Comparator**
Subjects with AE	13.6 (66/487)	8.6 (148/1729)	5.9 (112/1888)	12.1 (230/1897)
Adverse Events				
Vomiting	4.9 (24/487)	2.3 (39/1729)	1.1 (21/1888)	2.4 (92/1897)
Diarrhea	4.3 (21/487)	2.6 (45/1729)	1.8 (33/1888)	8.9 (169/1897)
Abdominal pain	1.4 (7/487)	1.7 (30/1729)	1.2 (22/1888)	2.0 (37/1897)
Nausea	1.0 (5/487)	0.4 (7/1729)	0.5 (9/1888)	1.2 (22/1897)
Rash	1.0 (5/487)	0.6 (10/1729)	0.4 (7/1888)	3.0 (57/1897)
Headache	0.0 (0/487)	0.1 (2/1729)	0.3 (5/1888)	1.1 (21/1897)

Of note in this table, vomiting was reported at a higher frequency in subjects who received the one-day azithromycin regimen. Diarrhea and nausea were also more frequent in this group, though even higher rates were seen in the comparator group. Higher rates of rash and diarrhea among patients in the comparator group are not surprising, since the comparator agents include beta-lactams and Augmentin in particular.

The following table notes the incidence of vomiting and diarrhea by day of onset and azi treatment group. Most of the vomiting noted with the one-day regimen occurs during the first day of treatment.

Percent (n/N) of Subjects Reporting Treatment-Related Vomiting and Diarrhea by Day and Treatment Group

Total Dose	**30 mg/kg**		
Dose Group	**30 mg/kg – SD (One-Day)**	**10 mg/kg x 3 (Three-Day)**	**10 mg/kg – Day 1 5 mg/kg – Days 2-5 (Five-Day)**
Vomiting			
Overall	4.9 (24/487)	2.3 (39/1729)	1.1 (21/1888)
Day 1	4.7 (23/487)	1.2 (21/1729)	0.5 (9/1888)
Day 2	0.2 (1/487)	0.6 (10/1729)	0.4 (7/1888)
Day 3	0.0 (0/487)	0.1 (2/1729)	0.2 (3/1863)
Day 4	0.0 (0/487)	0.0 (0/1729)	0.0 (0/1857)
Day 5	0.0 (0/487)	0.0 (0/1729)	0.0 (0/1851)
Diarrhea			
Overall	4.3 (21/487)	2.6 (45/1729)	1.8 (33/1888)
Day 1	1.6 (8/487)	0.5 (9/1729)	0.6 (11/1888)
Day 2	1.6 (8/487)	1.0 (17/1729)	0.4 (8/1888)
Day 3	0.4 (2/487)	0.5 (8/1729)	0.4 (7/1863)
Day 4	0.0 (0/487)	0.1 (1/1729)	0.2 (3/1857)
Day 5	0.0 (0/487)	0.1 (2/1729)	0.1 (2/1851)
SD = Single Dose; x3 = 3 days, x5 = 5 days			

Serious Adverse Events:

Of the 2152 subjects in the studies relevant to the claims, 8 reported serious adverse events. Five of the eight subjects received azithromycin and 3 received a comparator. The events reported by the azithromycin-treated subjects consisted of convulsions, diarrhea, enterocolitis, gastroenteritis, vomiting, dehydration, abscess, pleural effusion and pneumonia. Comparator-treated subjects reported fever, febrile convulsions, abdominal pain, gastroenteritis, vomiting, dehydration, otitis media, and upper respiratory tract infection. All serious adverse events reported by subjects in the studies relevant to the claims were considered unrelated to treatment by the investigator.

Current AOM Guidance

The following outlines the studies described in the current draft Guidance for Industry on AOM trials. This information is provided to outline the general recommendations made by the FDA to pharmaceutical firms performing AOM studies, and also to generate some discussion about these recommendations during the advisory committee meeting.

The draft Guidance recommends two trials, a clinical only study and a microbiologic study.

Clinical only study:

- Multicenter trial with rigid case definition
- Typically in children ≥6 months of age
- Baseline tympanocentesis not necessary; however, tympanocentesis of failures strongly encouraged

Microbiologic study:

- At least 2 investigators in geographically diverse areas
- Baseline tympanocentesis necessary for microbiologic etiology
- Repeat tympanocentesis strongly encouraged in therapeutic failures
- ≥ 25 *S. pneumoniae* (for PRSP, discuss with Division), ≥ 25 *H. influenzae*, ≥ 15 *M. catarrhalis* from the microbiologic study
- if clinical and microbiologic efficacy against three pathogens not adequate, restricted product to second line therapy

Case Definition

Clinical diagnosis of AOM at entry based on:

1. history and physical examination
2. pneumatic otoscopy findings:
   swollen bulging tympanic membrane (TM) which may be erythematous
   loss of light reflex and TM landmarks, abnormal TM mobility
3. tympanometry or acoustic reflectometry

Exclude patients with tympanostomy tubes, otitis externa but not those with perforated TMs

Primary efficacy endpoints

- Clinical and Microbiologic outcomes at test of cure visit (TOC) 2-4 weeks after study entry
- Microbiologic eradication presumed from the clinical response at TOC visit, for the majority of patients
- Negative culture at the on therapy visit not evidence of documented eradication

A complete copy of the draft guidance on AOM is provided as Reference 4.

References

1. Excerpted Information from Zithromax® Oral Suspension Label

2. Dagan R et al., "Bacteriologic and Clinical Efficacy of Amoxicillin/Clavulanate vs. Azithromycin in Acute Otitis Media" *Pediatric Infectious Diseases Journal* 19(2):95-104, February 2000.

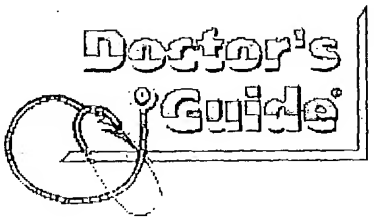
3. Dagan R et al., "Bacteriologic Efficacies of Oral Azithromycin and Oral Cefaclor in Treatment of Acute Otitis Media in Infants and Young Children" Antimicrobial Agents and Chemotherapy 44(1):43-50, January 2000.

4. FDA, Center for Drug Evaluation and Research, DRAFT Guidance for Industry "Acute Otitis Media – Developing Antimicrobial Drugs for Treatment" July 1998.

5. Marchant CD et al., " Measuring the Comparative Efficacy of Antibacterial Agents for Acute Otitis Media: The Pollyanna Phenomenon" *The Journal of Pediatrics* 120(1):72-77, January 1992.

6. Klein JO et al., "Microbiologic Efficacy of Antibacterial Drugs for Acute Otitis Media" *Pediatric Infectious Diseases Journal* 12(12):973-975, December 1993.

7. Carlin SA et al., "Host Factors and Early Therapeutic Response in Acute Otitis Media" *The Journal of Pediatrics* 118(2):178-183, February 1991.



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Title: **Single-Dose Zithromax (Azithromycin) As Effective As 10 Days Of Augmentin (Amoxicillin/Clavulanate) For Otitis Media**
URL: http://www.pslgroup.com/dg/1E12AE.htm
Doctor's Guide
September 14, 2000

NEW YORK, NY -- September 14, 2000 -- Pfizer Inc said that a new clinical study shows one single dose of Zithromax® (azithromycin for oral suspension) is as effective as Augmentin® (amoxicillin/clavulanate potassium), administered twice a day for 10 days, in treating acute otitis media in children.

Results of the multicenter clinical trial were presented recently at the Infectious Diseases Society of America (IDSA) annual meeting in New Orleans, La.

The study found that the treatment response of children with middle ear infections who received a single dose of Zithromax was clinically equivalent to the response of those treated with a 10-day course of Augmentin (86 percent vs. 88 percent, respectively; p=.620). Seventy-five percent of patients in both drug groups achieved treatment success upon observation at 32 days (p=1.000).

Zithromax is an oral antibiotic approved for use in children and adults; it achieves high and sustained levels in infected tissues making short course dosing possible.

The data necessary to include the single-dose regimen as an option for children with acute otitis media will be submitted to the U.S. Food and Drug Administration for review. The Zithromax product label currently includes a five-day, once daily dosing schedule that may make finishing medication easier than with conventional 10-day antibiotic regimens.

This randomized, double-blind trial conducted at nine U.S. centers evaluated 350 children between the ages of six months and 12 years with acute otitis media. Patients were randomized to receive either a 30 mg/kg single- dose of Zithromax oral suspension or 45 mg/kg of Augmentin twice a day for 10 days. The average age of children treated with Zithromax was 2.7 years and 3.4 years for those in the Augmentin group.

In the study, Zithromax (azithromycin) was generally well tolerated, with 17 percent of patients in the Zithromax drug group experiencing treatment-related adverse events as compared to 23 percent of those receiving Augmentin More children discontinued due to adverse events when taking Augmentin compared with Zithromax (six vs. two children, respectively). Additionally, twice as many children from the Augmentin group experienced diarrhea versus those receiving Zithromax (22 vs. 11 children, respectively). Vomiting, generally mild, occurred in seven children in each drug group.

"The results of this study indicate that a single oral dose of medication can accomplish what traditionally has taken up to 10 days; families and healthcare providers are likely to appreciate this alternative to conventional treatment," says Stephen Eppes, M.D., FAAP, associate director, Department of Pediatrics, Division of Infectious Diseases, Alfred I. duPont Hospital for Children, Wilmington, Del. "Likewise, the single-dose administration is likely to encourage improved patient compliance so that children are treated successfully the first time, reducing the risk of developing resistance to the antibiotic."

Because ear infections can occasionally cause temporary hearing loss and may impair speech and language skills, parents should understand the importance of seeking proper treatment. Physicians will often prescribe an antibiotic since bacteria are a frequent cause of ear infections. Most antibiotics require 10 days of multi-dose treatment. Children may not always finish the medication, a situation that can lead to possible treatment failure and may lead to the development of resistance to that medication.

Zithromax (azithromycin for oral suspension) is indicated for acute otitis media caused by Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. The most common side effects in otitis media are diarrhea/loose stools (2 percent), abdominal pain (2 percent), vomiting (1 percent) and nausea (1 percent).

Zithromax should not be taken by patients with hypersensitivity to azithromycin, erythromycin or any macrolide antibiotic.

Related Links: Zithromax (azithromycin) and Augmentin (amoxicillin/clavulanate potassium).

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